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CONTENTS

NUMBER 1, FEBRUARY, 1949

Pulmonary Insufficiency	ELFANOR DEF BALDWIN, M D, ANDRE COUR- NAND, M D, AND DICKINSON W RICHARDS, JR, M D	1
The Pathology of the Thymus in Myasthenia Gravis	BENJAMIN CASTLE- MAN, M D, AND EDGAR H NORRIS, M D	27
The Landry-Guillain-Barré Syndrome	WEBB HAYMAKER, M D and JAMES W KLRNOHAN, M D	59

NUMBER 2, MAY, 1949

The Etiology of Rheumatic Fever	A Review of Theories and Evidence BYRON H WAKSMAN, M D	143
Pulmonary Insufficiency	ELEANOR DEF BALDWIN, M D, ANDRE COUR- NAND, M D AND DICKINSON W RICHARDS, JR, M D	201

NUMBER 3, SEPTEMBER, 1949

Phagocytosis	L JOI BERRI, PH D AND TOM D SPIES, M D	239
The Course of Cirrhosis of the Liver in Patients Treated with Large Doses of Liver Extract Intravenously	ELAINE P RALLI, STEPHEN H LESLIE, GEORGE H STUECK, JR, HAROLD E SHORR, JAMES S ROBSON, DEL- PHINE H CLARKE AND BERTRAM LAKEN	301

NUMBER 4, DECEMBER, 1949

Rocky Mountain Spotted Fever	GEORGE T HARRELL	333	
Addison's Disease	S ZELIG SORKIN, M D	371	
Functioning Pancreatic Islet Cell Adenomas	A Review of the Literature and Presentation of Two New Differential Tests	E L CRAIN, JR, AND G W THORN	427

PULMONARY INSUFFICIENCY

II A STUDY OF THIRTY-NINE CASES OF PULMONARY FIBROSIS

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INTRODUCTION

This paper, the second of a series devoted to the study of pulmonary insufficiency in chronic pulmonary disease, presents the characteristic patterns of lung function as they are observed in cases with pulmonary fibrosis not complicated by any significant degree of pulmonary emphysema

Most of the previous physiological investigations on pulmonary fibrosis have been largely concerned with the defects of pulmonary function in cases with pneumoconiosis, in particular silicosis (1-6) A strikingly poor correlation between the degree of pulmonary dysfunction and the extent of the clinical and roentgenological findings was observed by all investigators In addition, the majority of the studies indicated that the severity of pulmonary insufficiency in silicosis as measured by changes in lung volume, diminution of maximum breathing capacity, unequal alveolar ventilation and arterial anoxia, was closely correlated with the extent of a coexisting emphysema Thorsten Bruce (5), however, in his extensive studies of a group of 197 silicotic subjects found emphysema to be a rare complication except in those cases having massive conglomeration of silicotic nodules In this group arterial anoxemia was only present in those cases with chronic pulmonary emphysema In the large non-emphysematous group he demonstrated frequent functional changes, such as restriction of the lung volume, of the maximum breathing capacity and an elevation of the respiratory position during forced hyperventilation Using the Nylm standard exercise test he could not demonstrate any increase in oxygen debt following the mild or moderate exercise He ascribed the marked hyperventilation that he observed in many of his subjects to reflex stimulation of the respiratory center, via the Hering-Breuer reflex There were, however, no measurements of the pCO_2 in the arterial blood to permit an evaluation of this factor in causing hyperventilation He demonstrated that his cases assumed an inspiratory position during hyperventilation, which would tend to stimulate the stretch receptors within the fibrosed walls of the bronchi and of the pulmonary vessels

The observation of arterial anoxia in cases with pulmonary fibrosis has been chiefly limited to cases suffering from a coexisting emphysema Knipping (7, 8) and Brauer (9) in their classifications of respiratory insufficiency describe two mechanisms, other than those commonly operating in emphysema, which may lead to arterial oxygen unsaturation

(1) Direct veno-arterial shunt of blood from the pulmonary arteries into pulmonary veins Both Knipping and Brauer cite as examples of this mechanism the arterial anoxia observed in pneumonia or bronchial obstruction

(2) Impairment of oxygen diffusion across the alveolar capillary membrane Brauer describes this mechanism as occurring in severe influenza, following gas poisoning, pulmonary edema and under certain experimental conditions

Very recently Wright (10) has reported physiological studies on a series of seven subjects with generalized pulmonary granulomatosis found in beryllium workers His significant findings were extreme hyperventilation during exertion, marked arterial anoxia both at rest and during exercise, a normal or only slightly decreased maximum breathing capacity and a generalized reduction of the total lung volume The $p\text{CO}_2$ of the arterial blood was measured in two cases, in one case with emphysema, it was markedly elevated, while in the other, with emphysema, it was low. He was able to show a low arterial oxygen tension and a high alveolo-capillary oxygen gradient in two cases He considered that the arterial anoxia was the result of an impaired oxygen diffusion across an abnormal alveolo-capillary membrane Histological examination of the tissue of the lung in two cases is said to have shown thickening of the alveolar walls

From this brief introduction, it is evident that with the exception of the cases of beryllium poisoning, arterial anoxia in pulmonary fibrosis has been rarely observed when chronic pulmonary emphysema was not present In the present study, based upon the analysis of 39 cases of pulmonary fibrosis of various origin and not complicated by a significant degree of pulmonary emphysema, various types of pulmonary insufficiency will be described

MATERIAL FOR STUDY AND CLASSIFICATION

The cases for this study were selected from a large group of functional studies performed in patients with chronic pulmonary disease, using the methods described and analyzed in the first paper of this series The basis of their selection was as follows

- 1 Roentgenological evidence of pulmonary fibrosis.
- 2 Absence of spirographic evidence of ventilatory obstruction
- 3 A residual air equal to or less than the predicted value

Thirty-nine cases with a variety of clinical diagnoses met these requirements These cases were divided into two groups according to the presence or absence of arterial oxygen unsaturation following exercise

Group I consists of 25 cases with an arterial oxygen saturation following exercise above 92 per cent, (the oxygen saturation is above 94 per cent in all but three cases). The clinical diagnoses were as follows:

- a 8 cases of silicosis
- b 6 cases of chronic pulmonary infection (2 cases with bronchiectasis and 4 cases with bilateral fibroid tuberculosis)
- c 5 cases of Boeck's sarcoid: The diagnosis was made in 2 cases by a positive skin biopsy, and was presumptive in the remaining 3 cases who had negative tuberculin tests and elevated serum globulins

d 2 cases of radiation fibrosis following mastectomy for carcinoma of the breast

e 1 cases of fibrosis of undetermined etiology (1 of them following the accidental intravenous injection of a gold preparation)

Group II consists of 14 patients with an arterial oxygen saturation following exercise below 92 per cent (The oxygen saturation is less than 81 per cent in all but 1 case) The clinical diagnoses were as follows

a 3 cases of pulmonary fibrosis associated with scleroderma

b 1 case with a history of exposure to the inhalation of sulfur dioxide

c 1 case with exposure to inhalation of asbestos fibers

d 2 cases of lymphangitic carcinoma

e 7 cases of pulmonary fibrosis following a mild influenza like respiratory infection

It should be noted that there was no overlapping of etiological factors in these two groups

RESULTS

The clinical features and the results of the physiological studies in each of these two groups may be described as follows

Group I

A Clinical characteristics In this group, the symptoms and the abnormal physical findings were, as a rule, limited and not correlated in any way with the extent of the disease as demonstrated by the x-rays. At rest, none of the patients was dyspneic and in only five cases, including the two cases with radiation fibrosis, was the dyspnea sufficiently severe to be incapacitating. The diagnosis was made purely on the basis of the abnormal x-ray findings in seven cases who presented negligible symptoms and physical signs. The remaining 12 cases complained of mild to moderate exertional dyspnea. The physical examination of many of the patients was entirely negative. Restriction of the respiratory movements was frequently present and particularly striking in the cases with radiation fibrosis. No cardiac enlargement was noted in any of the cases and electrocardiograms in the conventional leads available in 10 patients are normal. The roentgenological findings were varied. For example, the x-ray findings in the group of 8 silicotics who gave a history of exposure to silica dust for 10 to 45 years were as follows

3 cases with increased bronchovascular markings and beading

3 cases with diffuse nodular shadows

2 cases with conglomerate nodules

The 2 cases of radiation fibrosis presented dense, coarse, linear fibrosis with evidence of pleural retraction. The x-rays of the remaining cases showed either diffuse bilateral nodular fibrosis or coarse, linear fibrosis radiating out from the hilar regions. Typical x-ray pictures are shown in figures 1 to 5.

The majority of the cases belonging to this group were sent to the hospital only for evaluation of the pulmonary function and have not been reexamined

6 The mean oxygen consumption was normal at rest, during exercise and the five minute recovery period. There was no increase of the oxygen debt.

7 The mean arterial oxygen saturation at rest and following exercise was normal. The oxygen content of the arterial blood rose following exercise in all cases.

8 The mean arterial carbon dioxide tension during rest and following exercise was significantly lower than normal. It was found to be normal in only one case in the resting state, and in two following exercise. The mean pHs was

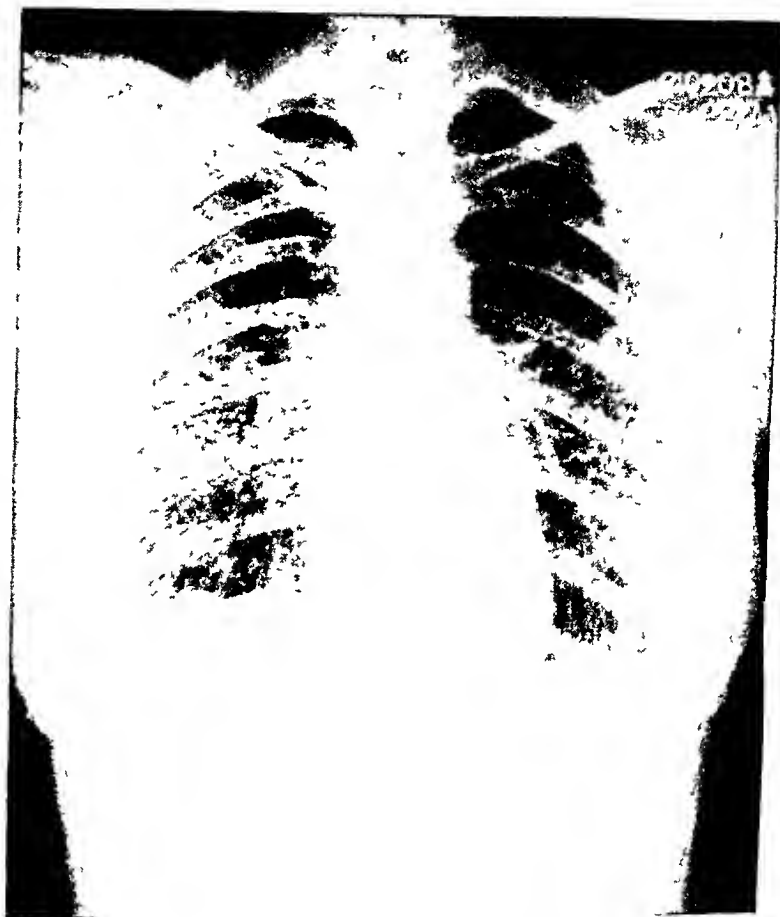


FIG 3 X-RAY PICTURE IN A CASE OF PULMONARY FIBROSIS OF UNKNOWN ETIOLOGY (CASE 1 SEE TEXT) PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP I WITH VENTILATORY INSUFFICIENCY

somewhat higher than normal at rest and following exercise and the mean alkaline reserve ($T_{4.0}$) was somewhat reduced.

C Comments It is apparent from these results that this first group of patients with pulmonary fibrosis suffers from a moderate ventilatory insufficiency without obvious disturbance of either the distribution or the diffusion factors. In cases with a normal maximum breathing capacity, the ventilatory insufficiency during exercise is related to the excessive ventilation, and the resulting decrease of breathing reserve below the threshold of dyspnea. In the majority

of cases, however, it is due to the combination of a restricted maximum breathing capacity and of hyperventilation. The low mean arterial carbon dioxide tensions both at rest and following exercise indicate that this is a true hyperventilation. The reduction in the alkali reserve (T_{40}) is an indication of the adaptation of the acid-base balance to the chronic hyperventilation. Its difference from the normal mean value has high statistical significance. In the



FIG. 4. X RAY PICTURE IN A CASE OF SILICO TUBERCULOSIS (CASE 2. SEE TEXT).
PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP I WITH VENTILATORY
INSUFFICIENCY

absence of a high $p\text{CO}_2$ or of a low oxygen arterial saturation, it appears that the hyperventilation is the result of reflex stimulation arising in the lungs.

A clear-cut correlation exists between the severity of the dyspnea as recorded in each patient's history and the size of his breathing reserve as measured during the first minute of recovery from the standard exercise. 14 patients who either denied or complained of only slight exertional dyspnea had a mean breathing reserve of 38 liters or 62 per cent of the mean maximum breathing capacity, 5 patients with moderate exertional dyspnea had a mean breathing reserve of 31 liters or 51 per cent of the mean breathing capacity, and in 5 patients complain-

ing of incapacitating exertional dyspnea the mean breathing reserve was 13 liters or 31 per cent of their mean maximum breathing capacity

D Individual cases Considerable individual variations occur in this group. The following three cases have been selected to illustrate this point

Case 1 M F, a 36 year old white housewife, was admitted to Sloane Hospital complaining of severe exertional dyspnea of six months' duration accentuated during the three weeks prior to admission. She was two months pregnant. She had done factory work in a dusty atmosphere. Her physical examination was essentially negative except for extreme hy-



FIG 5 X-RAY PICTURE IN A CASE OF RADIATION FIBROSIS (CASE 3 SEE TEXT)
PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP I WITH VENTILATORY INSUFFICIENCY

perpnea even at rest and the findings consistent with a two months pregnancy. Her chest x-rays showed a fine nodular fibrosis uniformly distributed throughout both lung fields (see figure 3). The costophrenic sulci were clear, the heart small and normal in contour. On fluoroscopic examination the diaphragms moved equally and well. The pregnancy was terminated with only slight subjective improvement. The clinical diagnosis was pulmonary fibrosis of unknown etiology. A few months after her studies the patient developed a rapidly progressing multiple sclerosis and has been bedridden for the past five years.

The data on pulmonary function of this patient (table 6), both before and after the termination of her pregnancy, revealed

1. A striking hyperventilation during and following exercise, associated with extremely low arterial carbon dioxide tension and normal oxygen saturation

TABLE I

Physical Characteristics in Thirty Nine Patients with Pulmonary Fibrosis

	GROUP I				GROUP II			
	Pulmonary fibrosis with ventilatory insufficiency				Pulmonary fibrosis with alveolo-respiratory insufficiency			
	No	Mean	S D	Range	No	Mean	S D	Range
Male								
Age in years	12	45	10	30-61	8	47	14	24-71
Weight in kilograms	12	72	11	56-90	8	59	0 3	56-68
Height in centimeters	12	169	9	154-183	8	173	16	161-187
Body surface area in m ²	12	1 82	0 3	1 52-2 12	8	1 70	0 1	1 56-1 81
Female								
Age in years	13	38	11	18-50	6	43	18	14-63
Weight in kilograms	13	54	8	43-66	6	52	6	43-61
Height in centimeters	13	160	8	144-172	6	163	6	151-170
Body surface area in m ²	13	1 51	0 1	1 37-1 79	6	1 54	0 1	1 40-1 70

TABLE 2

Lung Volumes and Maximum Breathing Capacity of Thirty-Nine Cases with Pulmonary Fibrosis

	PULMONARY FIBROSIS WITH VENTILATORY INSUFFICIENCY				PULMONARY FIBROSIS WITH ALVEOLO-RESPIRATORY INSUFFICIENCY				SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE MEANS
	No	Mean	S D	Range	No	Mean	S D	Range	P
Lung Volumes in per cent of Predicted Values									
Vital Capacity	25	75	22	38-113	14	46	14	25-69	< 0.004
Residual Air	25	76	20	36-110	14	69	15	37-99	0
Total Capacity	25	73	18	40-103	14	52	12	30-77	< 0.004
$\frac{\text{Residual Air}}{\text{Total Capacity}} \times 100$	25	27	6	17-40	14	33	7	24-45	0
Maximum Breathing Capacity in per cent of Predicted Value	25	75	22	44-117	14	83	24	47-145	> 0 5

$$* P = \text{probability derived from critical ratio} = \frac{\text{Mean 1} - \text{Mean 2}}{\sqrt{\frac{(S D_1)^2}{N_1} + \frac{(S D_2)^2}{N_2}}}$$

(Simpson, G. G. and Roe, A. *Quantitative Zoology*, pp 191, McGraw-Hill Book Co 1939)

2 Completely normal lung volumes and maximum breathing capacity

3 A breathing reserve of only 31 per cent of the maximum breathing capacity during the first minute of recovery from standard exercise associated with severe dyspnea, due to excessive hyperventilation. This symptom was not experienced after the third minute of recovery when her breathing reserve rose to 77 per cent of her maximum breathing capacity.

This pulmonary pattern illustrates ventilatory insufficiency in the presence of normal lung volumes and maximum breathing capacity, due to hyperventila-

TABLE 3

Ventilation and Breathing Reserve during the Standard Exercise Test and Index of Intra-Pulmonary Mixing in Thirty-Nine Cases with Pulmonary Fibrosis

	PULMONARY FIBROSIS WITH VENTILATORY INSUFFICIENCY				PULMONARY FIBROSIS WITH ALVEOLO-RESPIRATORY INSUFFICIENCY				SIGNIFI- CANCE OF THE DIFFER- ENCE BETWEEN THE MEANS
	No	Mean	S D	Range	No	Mean	S D	Range	P
Ventilation in L/min /m ² /B S									
Basal	25	4.1	0.6	3.1-5.5	14	5.3	1.0	4.1-7.6	> .05
1 min Standard Exercise	25	14.2	3.2	8.5-21.2	13	15.8	3.3	11.0-22.5	0
1st min Recovery	25	15.9	4.1	10.8-26.8	12	20.1	4.9	13.6-29.1	.01
Breathing Reserve Max Breathing Capacity $\times 100$									
Last min with dyspnea	15	61	18	15-85	9	66	7	56-76	0
First min without dyspnea	15	71	13	25-88	9	73	5	65-79	0
Index of Intra-Pulmonary Mixing Alveolar N ₂ per cent after 7 min pure O ₂ breathing	25	1.6	0.5	0.8-2.9	14	1.1	0.2	0.8-1.4	0

TABLE 4

Oxygen Consumption during the Standard Exercise Test in Thirty-Nine Cases with Pulmonary Fibrosis

	PULMONARY FIBROSIS WITH VENTILATORY INSUFFICIENCY				PULMONARY FIBROSIS WITH ALVEOLO-RESPIRATORY INSUFFICIENCY				SIGNIFI- CANCE OF THE DIFFER- ENCE BETWEEN THE MEANS
	No	Mean	S D	Range	No	Mean	S D	Range	P
Oxygen Consumption in cc / min /m ² B S									
Basal	25	135	12	116-166	14	144	19	114-175	0
1 min Standard Exercise	25	485	115	332-802	13	362	63	305-573	< .0001
5 min Recovery Period	12	1360		1189-1738	6	1550		1315-1920	
Oxygen Intake in cc /lit of Ventilation									
Basal	25	38.6	6.2	28.6-50.9	14	30.6	4.1	25.5-41.0	.005
1 min Standard Exercise	25	40.5	9.8	21.6-60.2	13	28.6	3.8	18.2-35.8	< .0004

tion alone. The cause of the increased stimulus to ventilation in this case is not entirely clear. Without demonstrable cardiorespiratory pathology or high

pCO₂ or low oxygen arterial saturation, an increased sensitivity of the Hering-Breuer reflex mechanism due to fibrotic changes about the bronchial tree is the most likely explanation. In this particular case there may be an additional, although remote, factor operating, namely, some central nervous system lesion. Attacks of hyperpnea are said to occur not infrequently in cases of multiple sclerosis.

TABLE 5

The Respiratory Gases of the Arterial Blood during Rest and following the Standard Exercise Test in Thirty Nine Cases with Pulmonary Fibrosis

	PULMONARY FIBROSIS WITH VENTILATORY INSUFFICIENCY				PULMONARY FIBROSIS WITH ALVEOLO RESPIRATORY INSUFFICIENCY				SIGNIFI- CANCE OF THE DIFF- ERENCE BETWEEN THE MEANS
	No	Mean	S.D.	Range	No	Mean	S.D.	Range	P
Oxyhemoglobin Saturation in per cent									
Basal	24	95	2.5	91-99	14	91	4.4	82-98	< .005
1st min Recovery	25	96	2.3	92-99	14	73	9.0	58-88	< .0004
Carbon Dioxide Content in Vols %									
Basal	23	46.1	3.0	39.0-52.6	12	48.6	3.8	44.6-55.8	0
1st min Recovery	23	44.0	3.1	34.6-49.2	12	45.8	3.1	43.7-53.4	0
Carbon Dioxide Tension in mm Hg									
Basal	15	34.2	4.1	26.3-42.4	7	43.6	2.6	39.6-46.4	< .0004
1st min Recovery	14	35.6	3.0	29.4-38.5	7	40.6	1.4	37.5-47.3	< .0004
Carbon Dioxide Content at 40 mm Hg (T ₁₀) in Vols %									
Basal	15	47.5	2.3	41.9-51.4	7	47.1	3.1	40.4-53.2	0
1st min Recovery	14	45.3	3.1	39.9-51.0	7	43.5	3.1	38.7-48.3	0
pHs									
Basal	15	7.46	0.17	7.39-7.52	7	7.41	0.17	7.37-7.43	< .0004
1st min Recovery	14	7.43	0.17	7.37-7.46	7	7.38	0.17	7.27-7.44	< .0004

Case 2 E Q, a 53 year old bronze worker, was admitted to the hospital complaining of right chest pain and a productive cough for one week. He admitted to only slight exertional dyspnea. Physical examination revealed the signs of cavitation over the right infraclavicular region and a hypertension of 170/100. His sputum on one occasion was positive for acid fast organisms. Chest x rays showed a marked conglomerate, nodular infiltration of both lung fields with cavitation on the right (see figure 4). The heart was not enlarged. On fluoroscopic examination both diaphragms moved well. The clinical diagnosis was silico tuberculosis. The patient was subsequently discharged to a sanatorium.

Pulmonary function studies revealed a relatively normal maximum breathing capacity (87 per cent of the predicted value, see table 6) in spite of a total lung

volume that was diminished to 50 per cent of the predicted value. Hyperventilation was present during all the periods of observation with a normal arterial oxygen saturation. In addition, the index of intrapulmonary mixing was elevated to 2.9 per cent, which must be considered abnormal in the presence

TABLE 6

Pulmonary Function of Three Individual Cases with Pulmonary Fibrosis Associated with Ventilatory Insufficiency

	CASE 1 M F		CASE 2 E Q		CASE 3 J H	
	Pulmonary Fibrosis		Silico-Tuberculosis		Radiation Fibrosis	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
I Lung Volumes in cc						
Vital Capacity	2984	2950	2118	3635	1275	2590
Residual Air	698	880	434	1555	542	1115
Total Capacity	3682	3830	2552	5190	1817	3705
$\frac{\text{Residual Air}}{\text{Total Capacity}} \times 100$	19	23	17	30	31	30
II A Maximum Breathing Capacity in lit /min	72	74	80	93	33	75
B Ventilation in lit /min /m ² B S						
Basal	4.1	3.2	4.7	3.9	3.7	3.4
1 min Standard Exercise	19.6	9.0	17.0	11.2	17.4	11.1
1st min Recovery	26.8	10.9	24.0	14.5	19.1	12.6
C $\frac{\text{Breathing Reserve}}{\text{Max Breathing Capacity}} \times 100$						
Last min with dyspnea	64		60		39	
1st min without dyspnea	78		74		dyspneic 5 min	
III A Index of Intra-Pulmonary Mixing						
Alveolar N ₂ %	0.8	<2.5	2.9	<2.5	2.1	<2.5
B Arterial Blood						
Oxyhemoglobin Saturation %						
Basal	99	96	94	96	91	96
1st min Recovery	96	96	97	96	96	96
Carbon Dioxide Tension in mm Hg						
Basal	29.4	43.7				
1st min Recovery	28.2	43.0				
IV Oxygen Consumption in cc /min /m ² B S						
Basal	119	141	133	132	116	129
1 min Standard Exercise	380	526	533	506	494	512

of a small lung volume. The breathing reserve was reduced to 43 per cent of the maximum breathing capacity during the first minute of recovery from the standard exercise and rose during the third minute of recovery to 74 per cent of the maximum breathing capacity when dyspnea ceased to be present.

This patient, as the previous one, illustrates a pattern of ventilatory insufficiency due to hyperventilation in the presence of a normal maximum breathing capacity. In addition, there was a marked, although uniform restriction of the total lung volumes, as well as a slight abnormality of the intrapulmonary distribution of respiratory gases. In the absence of $p\text{CO}_2$ measurements in the arterial blood, it is not possible to decide whether the Hering-Breuer reflex or any other stretch reflex originating in the lungs or pleura, was the sole cause of the hyperventilation.

Case 3 J. H., a 47 year old housewife, had suffered since youth from severe colds and bronchitis. Two years before admission she sustained a radical left mastectomy followed by massive doses of deep x-ray therapy over the left chest. Since this time her chief complaint was paroxysmal dyspnea. On physical examination her chest expansion was limited. The lower sternum moved inwards on inspiration. The breath sounds were diminished posteriorly over the lung bases. The heart was small, the pulmonic second sound was accentuated. The electrocardiogram was essentially normal. The chest x-rays revealed a bilateral linear fibrosis most accentuated over the right infraclavicular region (see figure 5). The left diaphragm was slightly higher than the right with a blunted left costophrenic sulcus. The clinical diagnosis was pulmonary fibrosis following radiation therapy, possibly associated with metastases from a breast carcinoma. The patient died of bronchopneumonia two months after study. There was no autopsy.

The pulmonary function studies (see table 6) revealed a marked restriction of the lung volumes to 49 per cent of the predicted value, with a residual air/total capacity ratio not significantly elevated above the predicted value in a woman of her age. Her maximum breathing capacity was likewise severely restricted. Hyperventilation during exercise and the first minute of recovery was so great that on the basis of calculation, there was no breathing reserve. Dyspnea continued well beyond the five minute period of observation. Remarkably enough, the arterial oxygen saturation was normal both during rest and following exercise. The $p\text{CO}_2$ was not measured.

The pulmonary function pattern of this patient illustrates severe ventilatory insufficiency as the result of considerable restriction of the maximum breathing capacity as well as hyperventilation. In spite of the marked restriction to her ventilation there was no evidence of alveolar respiratory insufficiency. She was the most abnormal case in the entire group. In the absence of $p\text{CO}_2$ measurement, the same comment as in the previous case is made concerning the mechanism of hyperventilation.

E Summary The significant findings in this first group of cases with pulmonary fibrosis without arterial anoxia is hyperventilation during moderate effort associated in most cases with a restriction of the lung volumes, of the maximum breathing capacity, or of both. This excessive ventilation is the result of an increased sensitivity of various reflex respiratory impulses, such as the Hering-Breuer reflex, stimulated by the fibrotic changes in and about the bronchial walls and vascular channels. It is not a compensating mechanism, for abnormalities of distribution and diffusion which affect the carbon dioxide tension, the oxygen saturation of the arterial blood and the acid-base equilibrium.

The symptom of dyspnea is only experienced in this group when the breathing

reserve is between 61 per cent and 71 per cent of the maximum breathing capacity. No correlation can be demonstrated between the severity of the physiological disturbance and the extent and degree of the fibrosis seen on the x-ray films.

Group II

A Clinical characteristics In contrast to the findings in Group I, the severity of the clinical symptoms of the patients belonging to this second group far outweighs the relatively limited physical findings and frequently the unimpressive x-ray changes. Early in their illness several had been diagnosed as suffering from a respiratory neurosis. The common complaints were: (a) severe incapacitating dyspnea on exertion, and in many cases at rest, (b) dry racking cough, (c) weakness and fatiguability. In the majority of cases the respiratory distress, the paroxysmal cough and cyanosis were striking. Clubbing of the digits was frequent. Physical examination of the chest revealed, as a rule, marked limitation of chest movements, several cases showed inspiratory retraction of the sternum, occasional atelectatic rales, and an accentuated pulmonic second sound. The heart was usually small, although terminally it became enlarged in three cases with associated evidence of cardio-circulatory failure. The electrocardiograms in the conventional leads were essentially normal in all cases. In the three cases who died of cardiocirculatory failure, electrocardiographic evidence of myocardial damage developed during the last months of life. A variety of x-ray pictures of this group is illustrated in figures 6 to 9. The chest x-ray of many of the cases shows a very fine reticulated fibrosis. The case with the history of sulphur dioxide inhalation presented a most unusual chest x-ray which showed, with the aid of a magnifying glass, a bilateral dissemination of multiple tiny areas of increased density 1 mm. in diameter, each with a small central area of radiotranslucency. Unfortunately, the x-ray pictures had been lost before any reproductions could be made.

The majority of the patients were examined only once during the course of their illness, with the notable exception of two cases who were followed for 5 to 6 years. Eight of the fourteen patients are known to be dead. The cause of death, except for one suicide, was pulmonary insufficiency associated with chronic congestive failure in three and with acute and sudden heart failure in one patient.

B Physiological observations The statistical data concerning the physical characteristics and the physiological measurements are tabulated in tables 1 to 5. As in the previous group, it is of interest to note the equal sex distribution.

The chief findings were as follows:

1. The lung volumes were greatly restricted in the majority of cases. The mean vital capacity was but 46 per cent, the total capacity 52 per cent of the predicted values. The mean residual air volume is also significantly reduced but the mean residual air/total capacity ratio (RA/TC) is somewhat elevated.

2. The mean maximum breathing capacity was relatively normal, 83 per cent of the predicted value, dropping below 75 per cent in only four of the cases.

3. The spiograms show that during the performance of the maximum breath-

ing capacity, the volume of each individual rapidly succeeding breath was equal to 60 per cent to 80 per cent of the vital capacity. There was no evidence of ventilatory slowing, obstruction or air trapping.

4 The hyperventilation during all periods of observation was extreme. In spite of the excessive ventilation, the mean breathing reserve during the last minute of dyspnea when present was 66 per cent of the maximum breathing capacity and the mean breathing reserve during the first minute of recovery

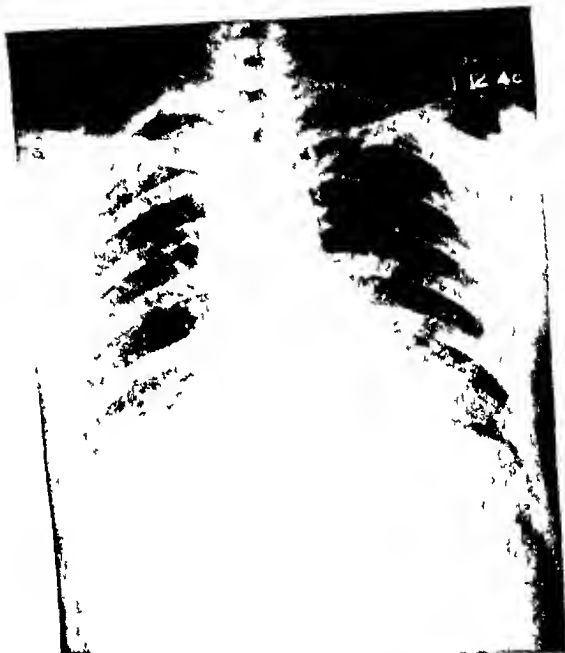


FIG. 6 X RAY PICTURE IN A CASE OF PULMONARY ASBESTOSIS, CONFIRMED BY ASBESTOS BODIES IN THE SPUTUM. PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP II WITH ALVEOLAR RESPIRATORY INSUFFICIENCY.

without dyspnea was, as in the previous group, 73 per cent of the maximum breathing capacity.

5 The mean index of intrapulmonary mixing was unusually low, with no case having a value above 1.4 per cent.

6 The mean oxygen consumption was normal at rest and considerably reduced during the minute of standard exercise. The oxygen consumption for the entire five minute recovery period could be collected in only six experiments because of the excessive ventilation which taxed the capacity of the 100 liter

spirometer. The mean value of these six observations, however, is high. It should also be noted that the rate of oxygen removal both at rest and during the standard exercise was extraordinarily low.

7 In contrast to the profound arterial anoxia following exercise, the mean arterial blood oxygen saturation at rest was only slightly reduced. In some individual cases, it was normal.



FIG 7 X-RAY PICTURE IN A CASE OF SCLERODERMA ASSOCIATED WITH PULMONARY INVOLVEMENT (CASE 4. SEE TEXT). PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP II WITH ALVEOLAR RESPIRATORY INSUFFICIENCY.

8 The mean arterial carbon dioxide tensions and pHs were normal both at rest and following exercise, in spite of the increased ventilation. The mean alkaline reserve (T_{10}) was slightly reduced, as in the first group.

C Comment. It is evident from these results that this group of patients suffers primarily from profound alveolar respiratory insufficiency with only minimal impairment of the ventilatory function. Inadequate alveolar ventilation as a cause of arterial anoxia can be ruled out on the basis of the normal pCO_2 . The residual an/total capacity ratio is somewhat elevated, suggesting some degree of pulmonary distension or emphysema, but the considerable hyperventilation during exercise probably compensates for any disturbance of distri-

bution that may be present. In addition, the spiographic records indicate that voluntary hyperventilation is performed at a normal respiratory level. The alveolar respiratory insufficiency in this group of cases must be the result either of a venoarterial shunt, an impairment of the diffusion of respiratory gases across the alveolar capillary interface, or a combination of both mechanisms.

It should be pointed out that the expressions, "venoarterial shunt," and impairment of diffusion, in the extreme cases are identical, the first describing the



FIG. 8. X RAY PICTURE IN A CASE OF INTERSTITIAL PNEUMONITIS (CASE 5 - SEE TEXT). PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP II WITH ALVEOLAR RESPIRATORY INSUFFICIENCY.

anatomical, the second the physiological condition. All gradations may exist between these two expressions depending upon the thickness of tissue interposed between the alveolar wall and the capillary.

D Individual cases. The following cases have been selected to illustrate the pattern of pulmonary function and because autopsy findings are available on each.

Case 4. R. B. a 65 year old white steam fitter, was admitted to the hospital complaining of severe dyspnea, extreme weakness and a mildly productive cough. He had become dur-

ing the preceding ten years, increasingly incapacitated by a slowly progressing exertional dyspnea. For four years he had noted progressive tightening of the skin of his hands and feet. On physical examination, respiratory distress was evident upon the slightest exertion, the chest movements were restricted and dullness and rales were present over both lower lung fields. His heart was not enlarged. The skin over his hands and feet was cold, firm and white. A prolonged PR interval was the sole electrocardiographic abnormality. Chest x-ray showed an extensive disseminated, bilateral, reticular fibrosis and a normal cardiac silhouette (see figure 7). Changes of the skin, typical of scleroderma, were found in the biopsy specimen. The patient ran a rapidly downhill course during his five months'



FIG 9 X-RAY PICTURE IN A CASE OF GRANULOMATOSIS OF THE LUNGS AND THE MEDIASTINAL GLANDS OF UNKNOWN ORIGIN (CASE 6. SEE TEXT). PHYSIOLOGICAL FINDINGS CHARACTERISTIC OF GROUP II WITH ALVEOLAR RESPIRATORY INSUFFICIENCY

stay in the hospital. He developed signs of cardio-circulatory failure. A second electrocardiogram disclosed a right preponderance, further prolongation of the PR and QRS intervals, as well as form changes indicative of myocardial damage. He died of pulmonary insufficiency complicated by congestive failure.

The data of pulmonary function studies (table 7) revealed (1) a marked reduction of the total lung volume, (2) a slightly increased residual air/total capacity ratio, (3) a relatively normal maximum breathing capacity, (4) hyperventilation, and (5) a low arterial oxygen saturation at rest. All the findings are typical of

the pattern in this second group. Although the patient was too ill to perform the standard exercise test, an arterial sample was obtained after some mild leg exercises which showed marked arterial anoxia. During right heart catheteri-

TABLE 7

Pulmonary Function of Three Individual Cases with Pulmonary Fibrosis Associated with Alveolar Respiratory Insufficiency

	CASE 4 R B		CASE 5 E A		CASE 6 V B	
	Pulmonary Fibrosis with Scleroderma		Chronic Interstitial Pneumonitis		Granulomatosis of Lungs	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
I Lung Volumes in cc						
Vital Capacity	1839	3490	1699	2510	825	2870
Residual Air	921	1560	739	1120	510	720
Total Capacity	2760	5050	2438	3630	1335	3590
$\frac{\text{Residual Air}}{\text{Total Capacity}} \times 100$	34	31	31	31	40	20
II A Maximum Breathing Capacity in lit/min	81	87	62	79	35	75
B Ventilation in lit/min/m ² /BS						
Basal	7.6	3.9	6.5	3.4	4.3	3.2
1 min Standard Exercise			14.7	11.1	11.1	9.0
1st min Recovery			20.3	12.6	13.6	10.9
III A Index of Intra Pulmonary Mixing Alveolar N %	1.4	<2.5	0.97	<2.5	1.1	<2.5
B Arterial Blood						
Oxyhemoglobin Saturation %						
Basal	91	96	82	96	86	96
1st min Recovery	81	96	58	96	63	96
Carbon Dioxide Tension in mm Hg						
Basal			40	43.7	35	43.7
1st min Recovery			42	43.0	40	43.0
IV Oxygen Consumption in cc/min/m ² BS						
Basal	165	132	139	129	137	141
1 min Standard Exercise			323	512	345	526
V Right Ventricular Systolic Pressures in mm Hg	70	<30			40	<30

zation studies, done before the appearance of symptoms of right heart failure, a marked pulmonary hypertension was found.

On autopsy, the gross inspection of the lungs revealed an extensive bilateral fibrosis which involved the entire subpleural and peripheral portions of the lungs,

a relatively normal appearing pulmonary parenchyma in both hilar regions. There were only a few sparse pleural adhesions and no enlargement of the mediastinal lymph glands. On microscopic examination (figure 10) the alveolar structure of the subpleural areas was replaced by a degenerative fibrosis containing much collagenous and hyaline matter but relatively well perfused with blood. The adjacent alveoli were dilated with thickened alveolar walls, therefore, the pulmonary capillaries were separated from the alveolar lining by a disposition of collagen and hyaline material. Bronchiectasis was also present in these areas. In the hilar region of both sides, the lung parenchyma was rela-

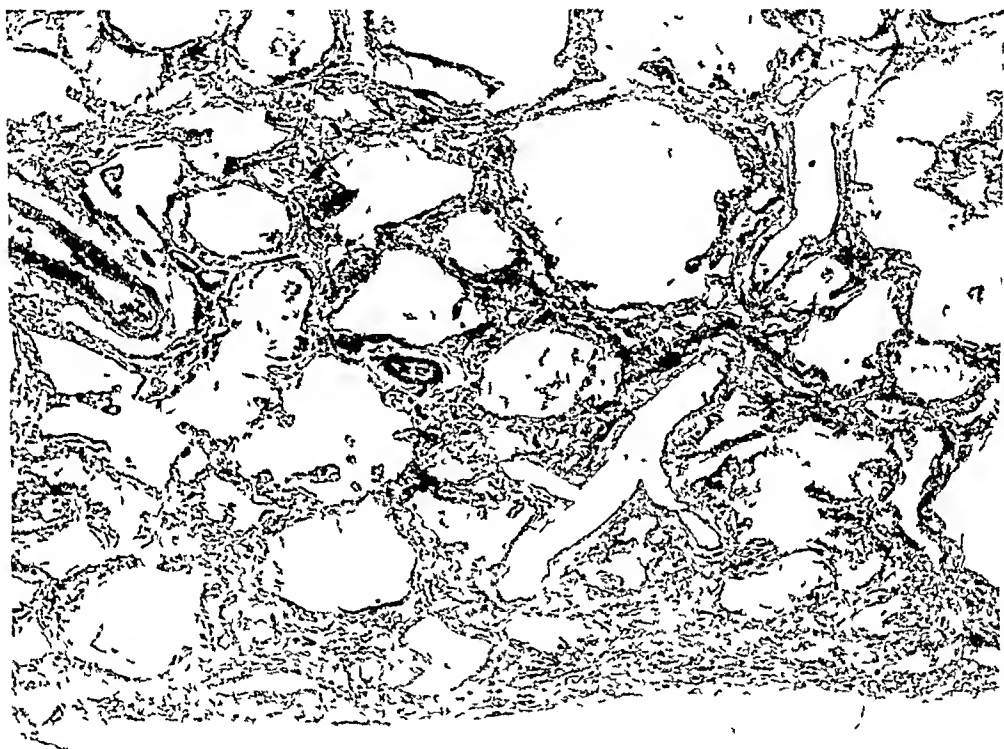


FIG 10 PHOTOMICROGRAPH 400 X H AND E

Section from subpleural region in a case of scleroderma (Case 4). Section reveals hyaline thickening of interstitium. Numerous cyst-like areas are present. The wall of the arteriole is thickened.

tively normal with minimal alveolar dilatation and in contrast to its complete disintegration in the subpleural region, the elastic tissue was normal. The pulmonary arterioles showed both intimal thickening and hypertrophy of the pars media. Considerable right ventricular hypertrophy and dilatation was present. The moderate fibrosis of the myocardium was that usually found in scleroderma.

The close correlation between the anatomical and physiological observations in this unusual case of scleroderma of the lungs is quite evident. The replacement of large areas of pulmonary parenchyma by fibrosis and the dilatation of

the remaining alveolar spaces are reflected in the marked restriction of the lung volumes and the moderately increased residual air/total capacity ratio. The absence of pleural adhesions, the presence of a fair proportion of lung with normal elastic tissue, the maintenance of the patency and mobility of the major bronchi, may well explain the large maximum breathing capacity observed during the patient's life. The pathological findings in the subpleural areas are consistent with the considerable degree of alveolo-respiratory insufficiency observed in this case. Finally, the observation of pulmonary arteriolar sclerosis accounts for the pulmonary hypertension. Whether the myocardial changes were to a great extent due to chronic anoxia, is a matter of speculation.

Case 5 L. A., a 63 year old white housewife, was first seen in October 1941, complaining of progressive shortness of breath on exertion for four months with recent dyspnea at rest. She was then moderately cyanotic. The chest movements were markedly diminished, although diaphragmatic motion was excellent. An accentuation of the pulmonic second sound was noted. A fine reticular bilateral fibrosis of both lung fields was found on the chest x ray (see figure 8). The cyanosis and dyspnea increased progressively until the patient became bedridden. In 1945, signs of profound congestive failure developed. Following a three months' stay in an oxygen room, she was able to return home on constant oxygen therapy and bed rest for approximately twelve months before her death.

The physiological data (table 6) were obtained three years before her death, when she was still able to undergo investigative procedures. The findings are also typical of the group, characterized by a restriction of the lung volumes, with a normal residual air/total capacity ratio, a relatively good maximum breathing capacity, a marked hyperventilation during all periods of observation and severe arterial anoxia both at rest and following exercise associated with a normal arterial carbon dioxide tension and pHs.

On autopsy, three years later, the pleural surfaces of the lungs were smooth and the mediastinal glands were not enlarged. On cut surface, the lungs presented a uniform appearance with an unusually distinct alveolar pattern and markedly thickened septa. On microscopic examination (figure 11) in contrast to the preceding case, there was no replacement of the alveolar architecture by fibrotic masses but rather a uniform thickening of the alveolar septa by fibroblasts, collagen fibers, intermingled with lymphocytes and wandering mononuclear cells. The pulmonary capillaries were separated from the alveoli by layers of connective tissue. The alveoli themselves were moderately dilated and lined by flattened layers of cuboidal cells and occasionally by hyaline plaques. An elastic tissue stain revealed very little elastic tissue, most of which appeared to be disintegrated. The heart was enlarged, weighing 340 grams, and the right ventricle was hypertrophied and dilated. The lack of pleural adhesions and of fibrosis about the bronchial walls and mediastinum are factors contributing favorably to the maintenance of a large maximum breathing capacity.

The striking pathological findings suggest that the alveolar respiratory insufficiency observed during life in this case was largely the result of impairment to the normal diffusion of oxygen across the greatly thickened alveolar capillary

a relatively normal appearing pulmonary parenchyma in both hilar regions. There were only a few sparse pleural adhesions and no enlargement of the mediastinal lymph glands. On microscopic examination (figure 10) the alveolar structure of the subpleural areas was replaced by a degenerative fibrosis containing much collagenous and hyaline matter but relatively well perfused with blood. The adjacent alveoli were dilated with thickened alveolar walls, therefore, the pulmonary capillaries were separated from the alveolar lining by a disposition of collagen and hyaline material. Bronchiectasis was also present in these areas. In the hilar region of both sides, the lung parenchyma was rela-

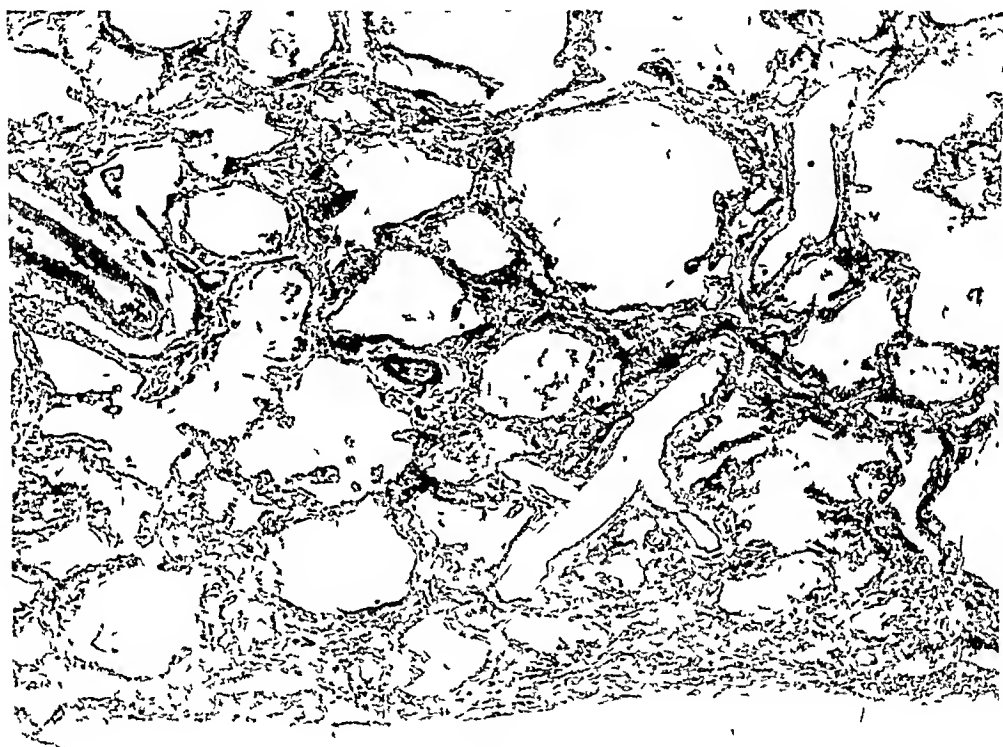


FIG 10 PHOTOMICROGRAPH 400 X H AND E

Section from subpleural region in a case of scleroderma (Case 4) Section reveals hyaline thickening of interstitium Numerous cyst-like areas are present The wall of the arteriole is thickened

tively normal with minimal alveolar dilatation and in contrast to its complete disintegration in the subpleural region, the elastic tissue was normal. The pulmonary arterioles showed both intimal thickening and hypertrophy of the pars media. Considerable right ventricular hypertrophy and dilatation was present. The moderate fibrosis of the myocardium was that usually found in scleroderma.

The close correlation between the anatomical and physiological observations in this unusual case of scleroderma of the lungs is quite evident. The replacement of large areas of pulmonary parenchyma by fibrosis and the dilatation of

during exercise and a considerable degree of arterial anoxemia in both these states. But they differ in the following aspects, namely, a moderately large residual air/total capacity ratio of 40 per cent, a considerable restriction of the maximum breathing capacity and only a moderate degree of hyperventilation during exercise and recovery. As in the first case, the pressure in the right ventricle indicated a marked systolic hypertension.

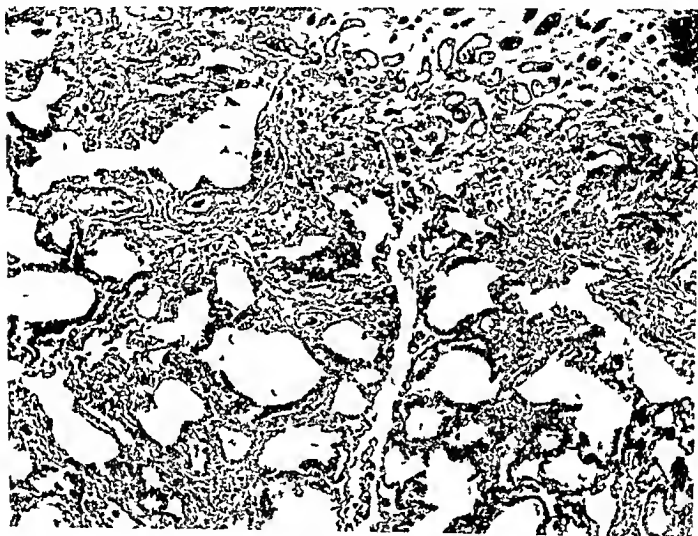


FIG. 12. PHOTOMICROGRAPH. 400 \times . II AND E.

Section from subpleural region in a case of pulmonary granulomatosis of unknown origin (Case 6). The section shows thickening of interstitial spaces with fibrous tissue and an infiltration of mononuclear cells and lymphocytes. Unidentified foreign body particles were visualized under polarizing microscope in these areas. The alveoli vary considerably in size.

On autopsy, dense pleural adhesions were found involving the entire right lung and the posterior lateral surface of the left lung. The lung was torn on removal. There were many cystic areas in the densely adherent right upper lobe separated by black, firm, fibrotic lung tissue. Elsewhere the cut surface of the lung disclosed many patches of fibrosis. On microscopic examination, these areas of fibrosis were found to be composed of vascular granulomatous tissue containing many mononuclear cells, fibroblasts and peppered with many small doubly refractile unidentified foreign bodies. The septae of the alveoli close to these fibrotic areas were considerably thickened. The mediastinal and bronchial glands were enlarged and frequently had a rubbery consistency but their histological appearance was not described. The heart was not enlarged.

interface. It is doubtful that the destruction of the elastic tissue was as marked, at the time of the physiological studies done four years prior to death, in view of the persistence of a relatively normal maximum breathing capacity and a normal residual air/total capacity ratio.

Case 6. V. B., a 27 year old negress, was admitted to the hospital complaining of progressive shortness of breath and cough productive of white sputum for 15 months following a severe chest cold. The patient worked as an electrical tester with occasional exposure to ozone and naphtha fumes and no known exposure to beryllium. The significant physical findings were respiratory distress following the slightest exertion, limitation of chest ex-

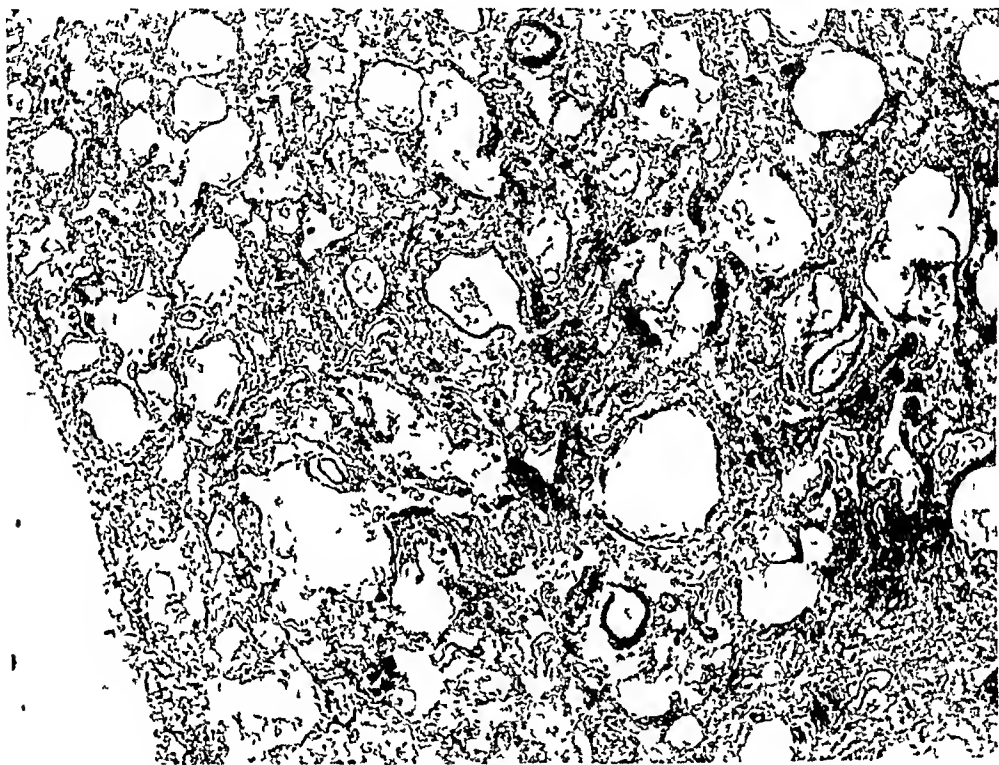


FIG. 11. PHOTOMICROGRAPH. 400 \times H AND E.

Section from subpleural region in a case of chronic interstitial pneumonia (Case 5). The section reveals diffuse interstitial infiltration of lymphocytes and mononuclear cells and vascular granulation tissue diffusely thickening the alveolar wall.

pansion, accentuation of the pulmonic second sound and clubbing of the fingers. Laboratory findings and sputum examinations were negative. Her electrocardiogram was normal with a right axis deviation. Chest x-ray revealed a small heart with a dilated right auricle, enlargement of the hilar lymph nodes and increased broncho-vascular markings (figure 9). The clinical diagnosis was pulmonary fibrosis of unknown etiology. The patient was followed for 8 months without any significant change. She suddenly died at home and was autopsied by the medical examiner.

The results of the pulmonary function studies on the patient (table 7) are characteristic of the group as a whole, in the considerable reduction of the total lung volumes, the maintenance of normal carbon dioxide tension at rest and

of the Pathology Department, Presbyterian Hospital who supplied the pathological information

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(240 grams) but dilatation of the right auricle and ventricle as well as slight right ventricular hypertrophy was noted

A good correlation was found between the anatomical and physiological observations. The findings of dense pleural adhesions and massive mediastinal lymphadenopathy as well as scattering of large fibrotic plaques throughout the entire lung fields gives an adequate anatomical explanation for the observed limitation of the maximum breathing capacity. The cystic areas and emphysema were reflected in the increased residual air/total capacity ratio. Finally, the alveolar respiratory insufficiency was mainly the result of the perfusion of the large areas of fibrosis that were not aerated, although poor ventilation of some of the cystic areas described in the autopsy cannot be ruled out.

E Summary The primary disability in this second group of pulmonary fibrosis is a profound alveolar respiratory insufficiency which results both from perfusion of large areas of fibrotic tissue which cannot be ventilated and impairment to the adequate diffusion of respiratory gases across a greatly thickened alveolar septa, or reduction in the area of alveolo-capillary interface.

Except in the cases with the greatest restriction of lung volumes, there was little or no impairment of the maximum breathing capacity. The striking hyperventilation may well be the result of reflex stimulation of pulmonary origin in addition to stimulus to the carotid body associated with arterial anoxemia. Right heart failure developed terminally in all cases that were followed.

Until the recent report of Wright on the pathological physiology of cases with chronic beryllium poisoning, the pattern of pulmonary insufficiency exhibited by this second group of cases was unique. Exposure to beryllium was unlikely in any of our cases but it should be noted that otherwise the history, physical examination, clinical course and autopsy findings on Case 6, V B, resemble very closely the one autopsied case of beryllium poisoning described by Hardy and Tabershaw (11).

CONCLUSIONS

On the basis of physiological studies 39 cases of pulmonary fibrosis without significant emphysema were divided into two clearly defined groups.

Group I represents primarily the pattern characteristic of ventilatory insufficiency without any obvious associated disturbance of either the distribution or diffusion of the respiratory gases. The clinical diagnoses of the group include silicosis, bronchiectasis, chronic fibroid tuberculosis, Boeck's sarcoid, and radiation fibrosis.

Group II presents predominately the pattern characteristic of alveolar respiratory insufficiency associated with a relatively normal ventilatory function. The clinical diagnosis of the group include scleroderma, exposure to sulfur dioxide and asbestos, lymphangitic carcinoma, and interstitial pneumonitis.

The authors gratefully acknowledge the cooperation of Dr Theodore J Curphey, Medical Examiner of Nassau County, of Dr David Spain, Pathologist, Columbia University Division, Bellevue Hospital, and Dr Dorothea Worcester,

of the Pathology Department, Presbyterian Hospital who supplied the pathological information

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THE PATHOLOGY OF THE THYMUS IN MYASTHENIA GRAVIS

A STUDY OF 35 CASES

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During recent years the improved technique in surgery of the mediastinum has led to wider use of thymectomy in the treatment of myasthenia gravis, thus the pathologist is now able to utilize surgical, in addition to post-mortem material in his study of possible relationships between the thymus and myasthenia gravis. The present paper is based upon a study of the thymus in 35 patients with myasthenia gravis observed at the Massachusetts General Hospital during the past forty years. In this group of cases there are 23 thymectomies,¹ 1 thymic biopsy, and 11 post-mortems, in 4 cases autopsies were performed at varying intervals following thymectomy.

The cases were easily divided from both a gross and microscopic standpoint into two main groups. The first 10 cases in which epithelial proliferation was prominent comprise one group (Table IV). The cases placed first in the table possessed a lesion that showed a maximal amount of epithelium and a minimal amount of lymphocytes, succeeding cases manifested somewhat lesser amounts of epithelium and a greater proportion of lymphocytic elements. In the remaining 25 cases (Table V) there was no evidence of epithelial proliferation but rather varying degrees of lymphoid follicle formation in the medulla.

That the thymic lesion in the first group is one that falls within the accepted limits of neoplasia, and that the thymus found in most of the cases in the second group is neither enlarged nor persistent but still abnormal are theses we shall attempt to defend.

STATISTICAL DATA AND REVIEW OF LITERATURE

Since 1917, when Bell (1) compiled the reported cases of myasthenia gravis in which thymic lesions were described, it has been customary to recognize three general groups, one in which a thymic tumor is found, a second in which the thymus is thought to be "persistent", "hyperplastic", or "enlarged", and finally those in which the thymus is thought to be normal. We have again surveyed the literature and have been able to get fairly good data on 295 cases.² Since the large majority of the reported cases, especially those without tumors, have inadequate microscopic descriptions, it was felt that a statistical analysis of these cases should be based on just two groups: tumors and nontumors. These together with our own series make available for analysis 330 cases. Of these, 97 are thymomas and 233 are nonthymomas.

¹ Most of the thymectomies were performed by Dr. Oliver Cope to whom we are very grateful for supplying us with his operative findings. We are also grateful to Dr. H. P. Viets for making the medical aspects of the cases available to us.

² We are grateful to Mr. Geoffrey Keynes of London who supplied us with statistical data on 112 patients on whom he has performed thymectomies, 11 were thymomas and 101 were non-neoplastic.

Incidence

It is very likely that considerable selection has operated in the cases reported in the literature, because these are largely individual case reports, instances in which a thymic tumor was found are more likely to have been recorded than those in which the thymus had no tumor

Also, with the increase in thoracic surgery, those patients without x-ray evidence of a thymic tumor are more apt to be operated upon. It is only very recently that the patient without evidence of a tumor is being subjected to thymectomy, thus allowing for a better evaluation of the incidence of thymoma to nonthymoma. Perhaps Keynes' (2) and Blalock's (3) figures of a 10 per cent tumor incidence or Good's (4) figures from the Mayo Clinic of 15 per cent are more accurate than the 30 per cent incidence of the entire series of reported cases

A review of all the thymic tumors at the Massachusetts General Hospital uncovered a few lymphomas and teratomas, but none of these came from myasthenics. What is more, the total group of thymic and mediastinal tumors includes only one case not associated with myasthenia gravis in which the lesion

TABLE I
Distribution per decade

	AGE							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	
Thymoma (no of cases)			14	28	28	24	3	97
Nonthymoma (no of cases)	2	34	91	67	27	8	4	233
Thymoma (percentage of cases)			14.5	29	29	24.5	3	100
Nonthymoma (percentage of cases)	1	15	39	29	11	3	2	100

resembled that found in our group of 10 tumors with myasthenia gravis. This was in a man of fifty, with symptoms of a mild, upper mediastinal syndrome and no symptoms, signs or laboratory evidence of myasthenia gravis, who had at operation a mediastinal tumor surrounding the great vessels. Microscopically, it fits in with Pattern I (to be described) of our thymoma series. It will be interesting to follow this patient to see whether he develops myasthenia gravis. It is well known that occasionally (we have had 2 and the Mayo Clinic 5 cases) there is definite x-ray or clinical evidence of a mediastinal tumor years before the onset of myasthenia symptoms.

Age

Table I shows the age distribution of 330 cases both by number and percentage of cases for each group. One striking finding is that only 14.5 per cent of the tumor cases occur before the age of thirty and none below twenty, while in the non-tumor group, 55 per cent occur before thirty and 16 per cent are under twenty. The thymomas are most common between thirty and sixty years of age and the nonthymoma cases between fifteen and thirty-five.

Sex

The sex distribution for all cases of myasthenia gravis classified according to age is given in Figure 1. There were 206 females and 123 males. From this figure it is apparent that up until the age of forty myasthenia gravis occurs much more often in the female. Of the 237 cases under forty, 70 per cent were females. After the age of forty, there were a few more males than females, 54 males and 48 females, but the difference may not be significant.

When the analysis of the sex distribution is carried out for the tumors and nontumors (fig. 2) one observes that the thymomas occur more often in the male (60 per cent). One should point out, however, that myasthenia gravis is a bit more common in the male after forty years of age and since thymomas are found

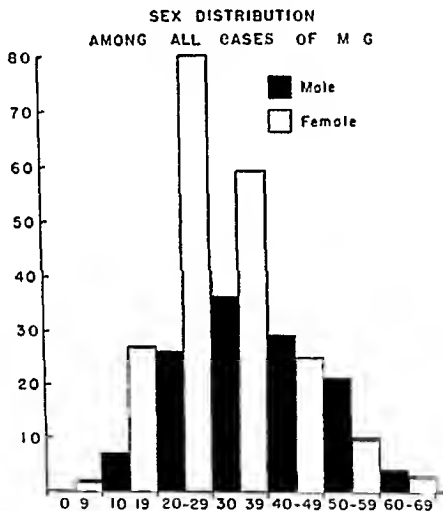


Fig 1

more often in the older age group, perhaps the sex difference between thymomas and nontumors may be merely a matter of age difference.

Duration of symptoms

The striking finding is that the duration of the symptoms in the thymoma cases is much shorter than in the nontumor cases (Table II). About half the thymoma cases had symptoms for one year or less in contrast to 30 per cent of the nontumor cases. Also, only 18 per cent of the thymoma patients had symptoms for over three years, while this was true for 40 per cent of the nontumor cases.

Since early operation may affect the natural course of the disease, Table III, dealing with only nonoperative autopsy cases, was prepared. Here also the duration of symptoms in the thymoma cases is short, 55 per cent of the thymoma

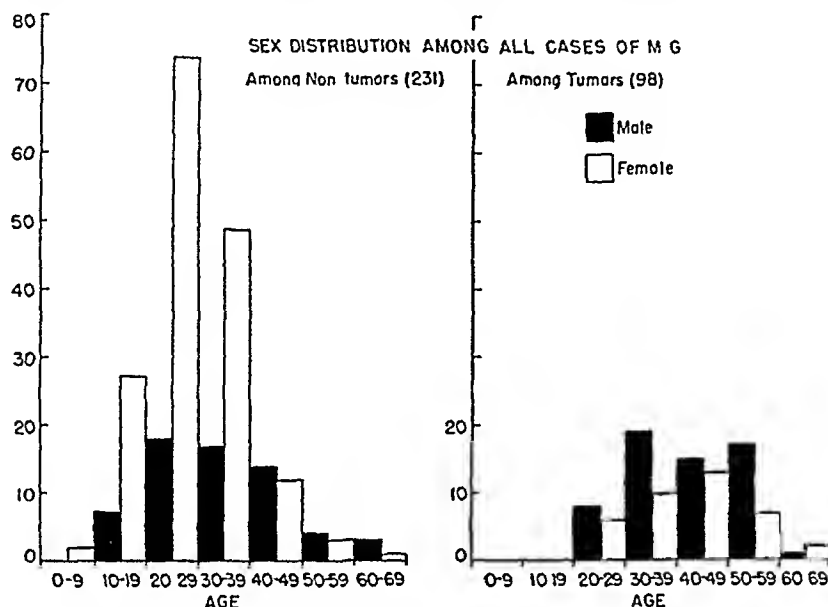


FIG 2

TABLE II

Duration of symptoms (307 cases)

	CASES PRIOR TO OPERATION OR AUTOPSY			
	Under 1 yr	1-3 yrs	Over 3 yrs	Total
Thymoma	43 (50%)	27 (32%)	15 (18%)	85
Nonthymoma	65 (30%)	67 (30%)	90 (40%)	222

TABLE III

Duration of symptoms of 88 autopsy cases

	1 YR OR LESS	1-3 YRS	OVER 3 YRS	TOTAL
Thymoma	22 (55%)	9	9	40
No thymoma	17 (35%)	16	15	48
Total	39	25	24	88

cases having symptoms for one year or less versus 35 per cent for the nonthymoma cases

CASE REPORTS

Group A thymoma (see Table IV)

Case 1 (L F , 377,915) A male, twenty-eight years old, with symptoms of myasthenia gravis for one and one-half years

TABLE IV

Thymomas

NO	INITIALS	SEX	AGE	DURATION OF SYMPTOMS	OP	AUT	THYMUS					
							Size	Wt	Mi	Pattern	Lim of thymus	C arm center in rim
				years			cm	gm				
1	I I	M	28	1½	O	—	1 × 3 × 2			I II III	+	+
2	J J	M	41	1	O	✓	3 × 2			I	+	+++
3	M D	F	17	1	O	—	8 × 6 × 1	55		II	+	+
4	I H	F	31	¾	O	—	fills mediast			I III	—	—
5	J G	M	45	11	—	✓	fills mediast			II	—	—
6	H R	M	36	2½	O	✓	8 × 6.5 × 2.5	50		II	—	—
7	J M	M	57	1	—	✓	2 × 2 × 2			II	+	+
8	J V	M	28	3	O	—	9 × 5 × 1.5	97		II	+	—
9	C K	F	51	2	—	✓	7 × 1 × 1			II	+	0
10	J S	M	18	?	—	✓	7.5 × 5.5 × 2.5			III	+	+

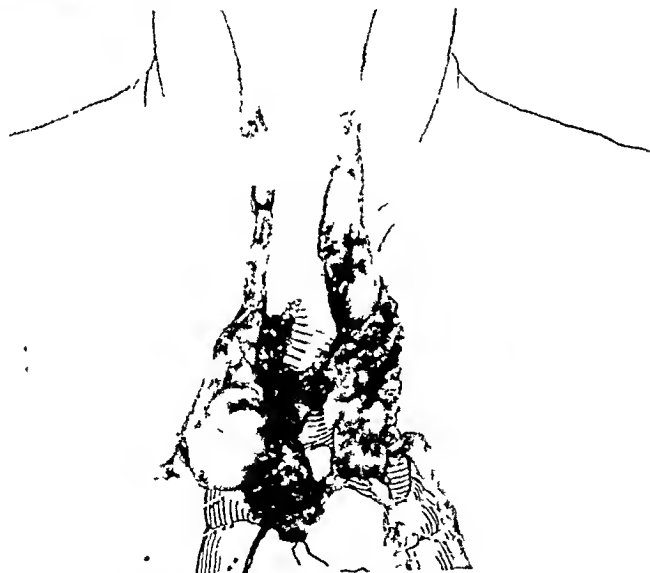


Fig 3 Case 1. Resected thymoma and surrounding thymus, placed on schematic drawing of chest to demonstrate location in mediastinum

Operative findings and gross description of surgical specimen. A tumor of the thymus was located in front of the right pulmonary hilum anterior and lateral to the right auricle (fig 3). Thymic tissue was present on both sides of the tumor.

The specimen consisted of 2 elongated, roughly U shaped pieces of tissue that weighed

40 grams The tissue of the two arms was lobulated and reddish yellow In the lower portion of the right arm was a firm, well-encapsulated, irregularly oval mass $4 \times 3 \times 2$ cm, the cut surface was whitish gray, homogeneous and divided into lobules by connective tissue bands

Microscopic findings General structure of the tumor The tumor was surrounded by a thick capsule of dense fibrous tissue from which septa arose to partially divide the tumor into lobules of variable size and shape (fig 4) The septa became attenuated and more and more delicate in the deeper parts of the tumor so that the outline of the lobules became less definite and the tissue of adjacent lobules tended to become confluent In places just outside but intimately associated with the capsule of the tumor, bits of uninvolved thymic tissue were present



FIG 4 Case 1 Photomicrograph at low magnification showing lobulation of tumor Note variation in density of lobules, the pole on the right is predominantly epithelial Note also a rim of normal thymus outside the capsule $\times 10$

The structural make-up of the lobules of the tumor showed great variation due to the varying proportions of epithelial cells and lymphocytes, but in general each individual lobule was the same throughout At times the appearance of two adjacent lobules was very different, the transition from one pattern to another often being abrupt (fig 5) On the basis of these structural variations three distinctive histological patterns have been recognized

Pattern I The tissue is made up largely of epithelial cells arranged in the form of an irregular network of anastomosing cords, whose size and form appear to be determined by the size and arrangement of the capillaries and sinusoids to which the cords are related Here and there, through an exaggeration of this pattern, an adenomatoid arrangement of epithelial cords is produced (fig 6) Along and about the vascular elements and in the tissue spaces between the epithelial cords a few lymphocytes are lined up in rows or are sparsely present in small groups Where the lymphocytes are sparse they appear to have been squeezed out by the disproportionate overgrowth of the epithelium (fig 7)



FIG 5 A higher power of Figure 4, showing two adjacent lobules, one with epithelial cells and lymphocytes in about equal numbers (Pattern II) and the other with a predominance of lymphocytes (Pattern III) $\times 135$

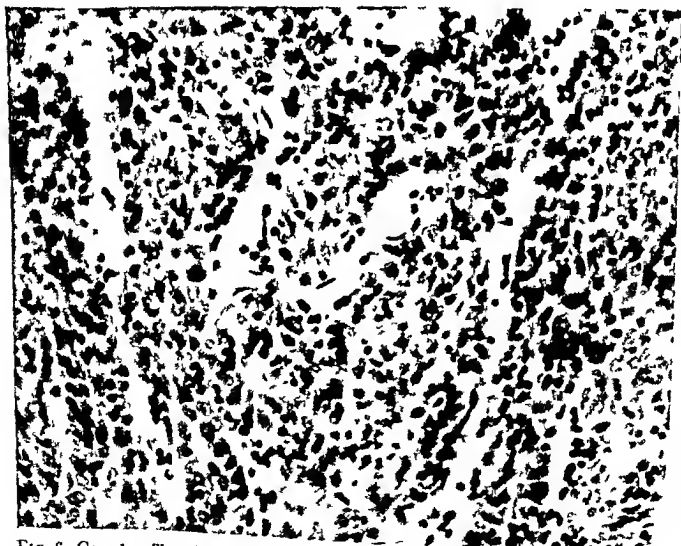


FIG 6 Case 1 The adenomatous part of the tumor (Pattern I) in which epithelial cells are present

Pattern II In this pattern the amount of the epithelial and lymphoid elements is nearly equal, intermediate between Patterns I and III (fig. 8)

Pattern III Here the tumor is made up largely of lymphocytes. The lymphocytes are crowded together and predominate so greatly in numbers that the less numerous epithelial cells are partially obscured, these latter are disposed in the form of a loose syncytium, and it is into the wide, intercellular interstices of this syncytium that the lymphocytes are crowded (figs. 5 and 17). There is no attempt at germinal center formation.

Multiple sections of the tumor from Case 1 indicate that most of the tumor was made up of tissue corresponding to Patterns I and II in about equal proportions, only a small part of the tumor showed the structure of Pattern III.

Apparently the tumor lobules represent enlarged thymic lobules, for they had the same general form and arrangement as lobules of a normal thymus. However, in the tumor

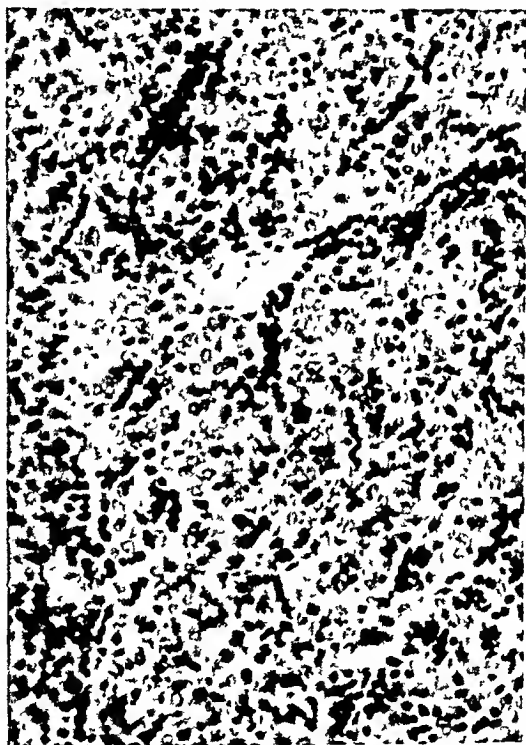


FIG. 7. Another area of Case 1 with thin rows of lymphocytes apparently being squeezed out by the epithelial cells. $\times 180$

lobules there was no regular, topographical organization of cortical and medullary portions. No adipose tissue and no Hassall's corpuscles were found within this tumor. In the deeper parts of the tumor liquefactive, degeneration cysts were noted in considerable numbers.

Cytology of the tumor The epithelial cells had irregular cell bodies that were joined, broadly or narrowly, by more or less attenuated syncytial processes with neighboring cells. For the most part the outlines of the epithelial cells were indefinite, since cell walls were poorly developed. The cytoplasm was finely granular and faintly acidophilic or amphophilic. The nuclei of the epithelial cells were most characteristic (fig. 9), typically the nucleus was a relatively large ovoid body, outlined by a delicate, but very distinct nuclear wall. Small masses of chromatin tended to be arranged next to the nuclear wall and a few similar granules were scattered irregularly through the nucleus. Delicate strands of chromatic material separated the nucleus into compartments that were filled with clear nuclear sap. Each nucleus contained one or sometimes two, prominent and densely stained nucle-

oli. The chief variations from this nuclear type had to do with changes in its shape. Not a few nuclei were elongated ovoids, some were notched or indented, while others were irregularly angular. No mitoses were observed in this tumor. Thus, in general, the epithelial cell and its nucleus stained palely and its vesicular appearance contrasted sharply with the more deeply stained lymphocytes. The latter had no visible, stainable cytoplasm. The round nucleus was outlined by a distinct nuclear wall and contained several blocks of dense chromatin, the nuclear sap was distinctly basophilic and the entire nucleus very dark.

Description of the uninvolved thymus. The thymic tissue adjacent to the tumor's capsule and that located in the mediastinum, but less closely related to the tumor, had the same structure, it resembled the moderately involuted thymus of an adult. In it the lobular arrangement was definite and cortical and medullary portions were easily recognized, the

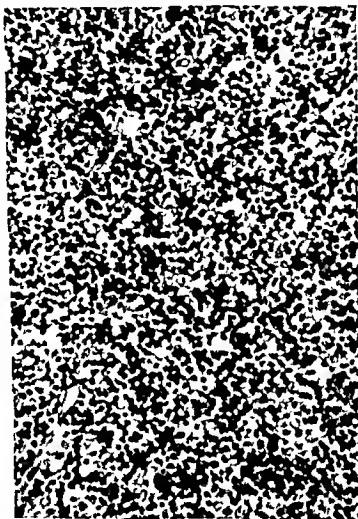


FIG 8 Case 3. A good example of Pattern II with about equal distribution of epithelial and lymphocytic cells. $\times 180$

mass of the medulla exceeded that of the cortex. Hassall's corpuscles were present in normal numbers. In one section a well defined germinal center was present in the medulla.

Case 2 (J. L., 357,689). A male, forty one years old, with symptoms of myasthenia gravis for one year. At operation no tumor was found in the mediastinum. Such thymic tissue as could be recognized was removed, it weighed 8.4 grams. The patient died on the third postoperative day of marked pulmonary congestion and edema.

Autopsy findings. At the root of the left lung anterior to the bronchus there was a white, firm nodule 2 x 3 cm. that was adherent on its posterior surface to the anterior aspect of the bronchus.

Microscopic findings. Except that the lobules were smaller and more completely separated by septal bands (fig. 10), the general architecture of this tumor was like that of Case 1. No uninvolved thymic tissue was found adherent to the capsule. On one surface the tumor

was adherent to the visceral pleura. Throughout there was a very high proportion of epithelial cells similar to those described in Case 1 (fig 11)

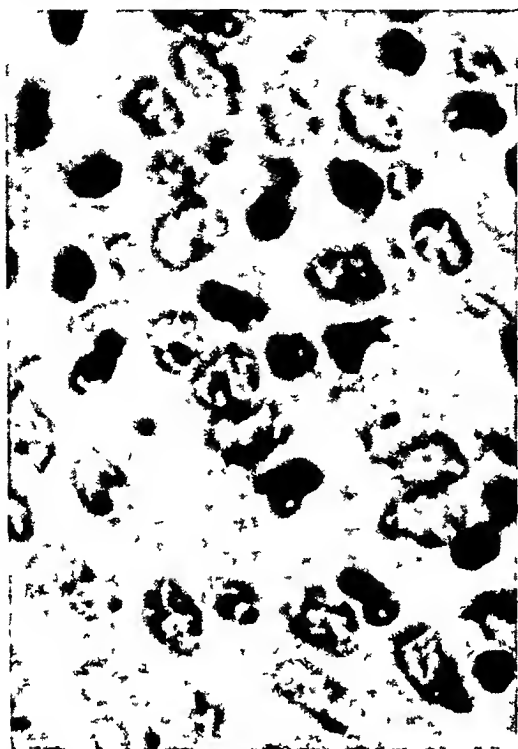


FIG 9 Case 1 A high power view showing details of the epithelial cells. Note their variation in shape but absence of anaplasia. A few scattered lymphocytes are present $\times 400$

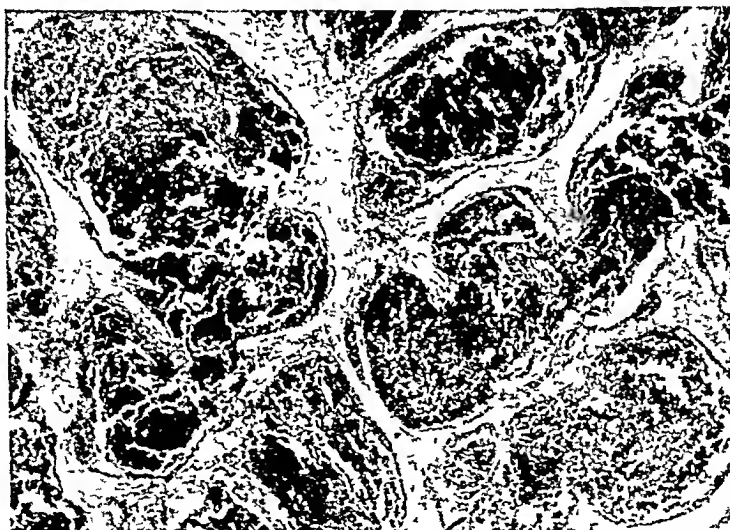


FIG 10 Case 2 Low magnification of ectopic thymoma at root of left lung showing lobular arrangement $\times 25$

Description of the surgical specimen The thymic tissue was moderately involuted, the lobules being rather widely separated by adipose tissue (fig 12). In it the lobular arrange-

ment was definite and cortical and medullary zones were easily recognized, Hassall's corpuscles were present in normal numbers, many germinal centers were seen in the medulla



FIG 11 High magnification of Figure 10 showing both epithelial and lymphocytic cells
 X 400

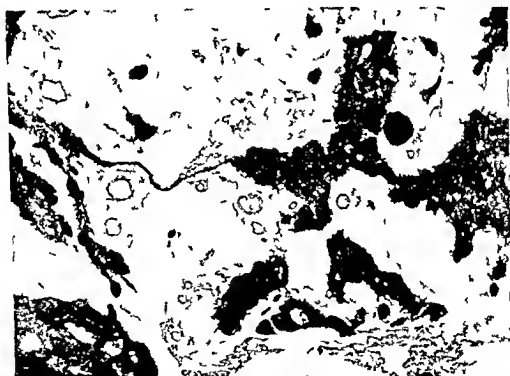


FIG 12 Case 2 Moderately involuted thymus removed surgically before the thymoma shown in Figures 10 and 11 was discovered at autopsy Arrows point to some of germinal centers Cystic foci are Hassall's corpuscles X 12

Case 3 (M D , 550 751) A woman, forty seven years of age, with symptoms of myasthenia gravis for one year prior to her operation X ray revealed a mass in the anterior mediastinum

Operative findings and gross description of surgical specimen A small, normal appearing, fatty thymus was exposed in front of the aorta, but to the left of the aorta, extending down along the pleura and over the pulmonary artery was an irregular mass that measured 8 x 6 x 4 cm In two places the left pleura was densely adherent to areas of necrosis in the tumor The left phrenic nerve ran within the capsule of the tumor and had to be dug

out The tumor was removed together with the adherent pleura, and a biopsy taken from the uninvolved thymus

The specimen was an encapsulated, slightly lobulated, moderately soft, grayish-pink mass that weighed 55 grams (fig 13) On section the tissue was very soft and a few small cystic spaces filled with clear fluid were present (fig 14)

Microscopic findings The capsule, stromal septa, and lobules were much like those seen in Case 1 Throughout epithelial and lymphocytic elements were present in nearly equal amounts, and the tumor conformed to Pattern II (fig 15) No mitoses were seen Liquefactive, necrotic cysts were present in the central part of the tumor, and an occasional Hassall's corpuscle was found within the tumor tissue



FIG 13 Case 3 External view showing lobulation and well defined encapsulation

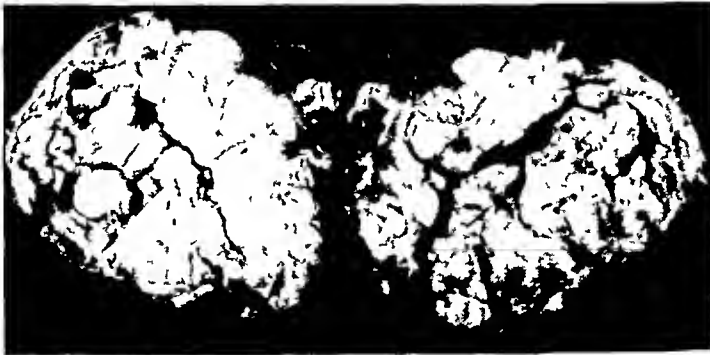


FIG 14 Cut surface of tumor shown in Figure 13 showing lobulation and cystic degeneration

Description of the biopsy of uninvolved thymus The thymus was markedly involuted Cortical and medullary zones were not distinct and the delicate lobules were widely separated by adipose tissue A few questionable germinal centers were present in the medulla

Case 4 (E H , 601,871) A woman, age thirty-one, with mild symptoms of myasthenia gravis for three and a half years A mediastinal tumor was seen by x-ray at onset of symptoms and three series of x-ray treatments were given without relief Symptoms recently increased in severity and the mediastinal shadow had increased in size

Operative findings The tumor was enormous and consisted of two parts, one lying in the mediastinum embracing the ascending aorta and extending to the anterior chest wall and from the level of the heart up almost to the base of the neck Thus portion of the

tumor was dense and firm and could not be dissected free from the aorta or any of the adjacent tissues to which it was adherent. The second part of the tumor was very soft and vascular, arising from the dense portion and extending upward and posteriorly into the left chest, growing through the mediastinal pleural reflection and directly into the adjacent surface of the upper lobe of the lung.

Microscopic findings The biopsy of the firmer portion of the tumor was predominantly epithelial and fits in with Pattern I (fig 16). Lymphocytes were scattered among the epithelial cells and often were collected around a large group of epithelial cells. Dense fibrous connective tissue bands surrounded islands of the epithelial cells and probably account for the firmness of the tumor grossly. The epithelial cells were similar to those described in Case 1, but unlike any of the other cases, an occasional mitosis was seen. The biopsies from the grossly softer areas were comprised predominantly of lymphocytes with

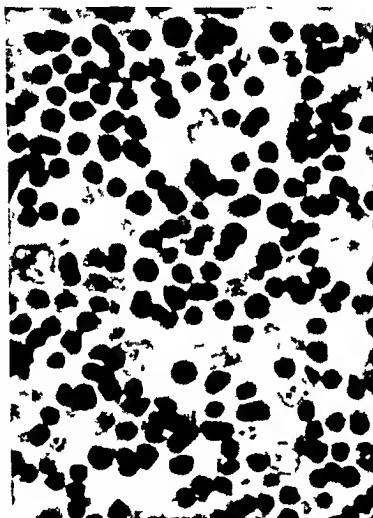


FIG 15 Photomicrograph of tumor shown in two previous figures. Note the characteristic epithelial cells scattered among the lymphocytes. $\times 300$.

a few scattered epithelial cells conforming to Pattern III (fig. 17). Here also an occasional mitosis was seen in the epithelial cells between the lymphocytes. No evidence of normal thymus or Hassall's corpuscles was observed.

Case 5³ (J. C., B. I. H.) A male, forty-five years of age, with myasthenia gravis for eleven years. Seven and one-half years prior to death (three and one-half years after onset of symptoms) a mediastinal mass was recognized by x-ray. According to the roentgenologist the mediastinal tumor increased in size, especially during the last year of his life. X-ray therapy was given over the mediastinum during the latter months. On several occasions there had been a left hydrothorax, but no malignant cells were found in the fluid withdrawn. Death occurred from respiratory failure.

³ The authors wish to thank Dr. M. J. Schlesinger of the Beth Israel Hospital, Boston, for permission to include this case.

Autopsy findings The mediastinum was filled with tumor tissue, which extended from the manubrium to the aorta and into the posterior mediastinum, where it formed a chain

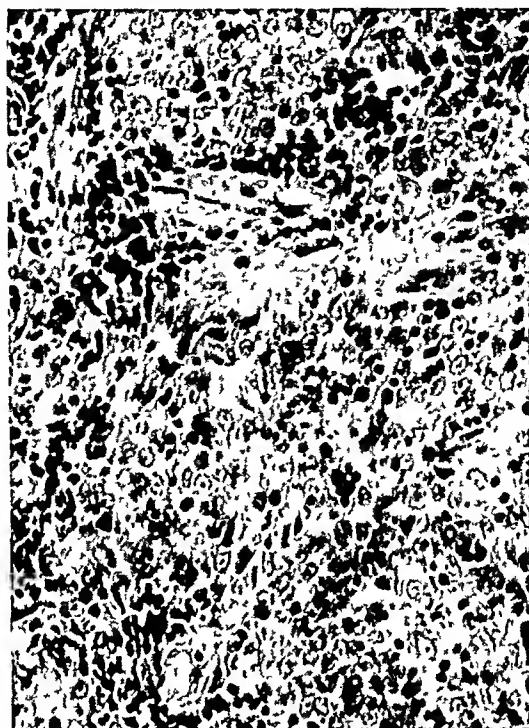


FIG 16 Case 4 There are large islands of epithelial cells with a scattering of lymphocytes $\times 200$

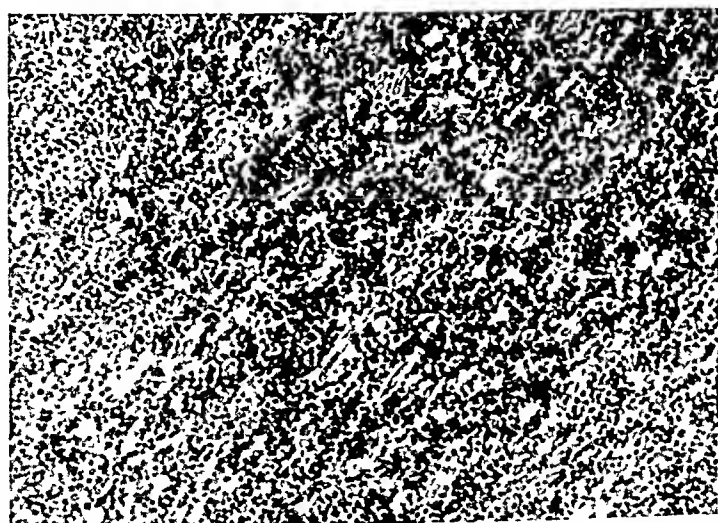


FIG 17 In another portion of the tumor in same case as Figure 16 there is a predominance of lymphocytes $\times 100$

of nodular masses that surrounded the aorta and esophagus. However, there did not appear to be any encroachment upon the great veins or the trachea. Anteriorly, lobules of the mediastinal tumor seemed to have extended into the substance of the left lung. On

section the tumor was made up of fleshy, gray pink, soft tissue and some parts appeared to be undergoing necrosis

Microscopic findings Despite the long period of time that this tumor was known to have been present, and despite its size and extensiveness, it was remarkable to observe how well the lobular arrangement, similar to that of the normal thymus, had been preserved

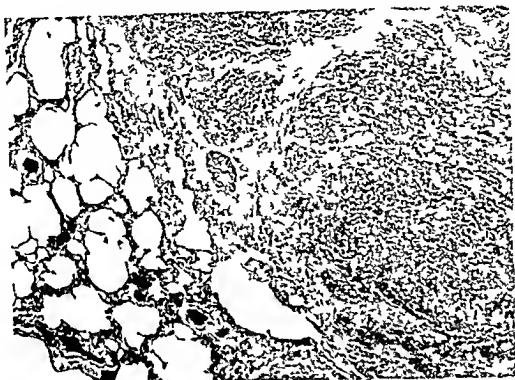


FIG 18 Case 5 An example of extension of tumor to visceral pleura Note the preservation of the lobular arrangement of the tumor $\times 15$



FIG 19 Another field of Case 5 showing orderly invasion of lung parenchyma $\times 65$

in peripheral parts of the growth This morphologic feature was particularly well seen in those parts of the tumor that were encroaching upon the pleura and the lung (fig 18) On one surface the tumor had broken through its capsule and through the adjacent visceral pleura to invade the lung This extension into the lung, however, was not a wild invasion, but had more the appearance of an orderly encroachment (fig 19) The histologic structure was rather uniform throughout The epithelial cells and lymphocytes were present in approximately equal amounts (Pattern II) In cells of the epithelial type a considerable

number of hyperchromatic, macronuclei were present (fig 20) No uninvolved thymic tissue was found either in the gross dissection or microscopically

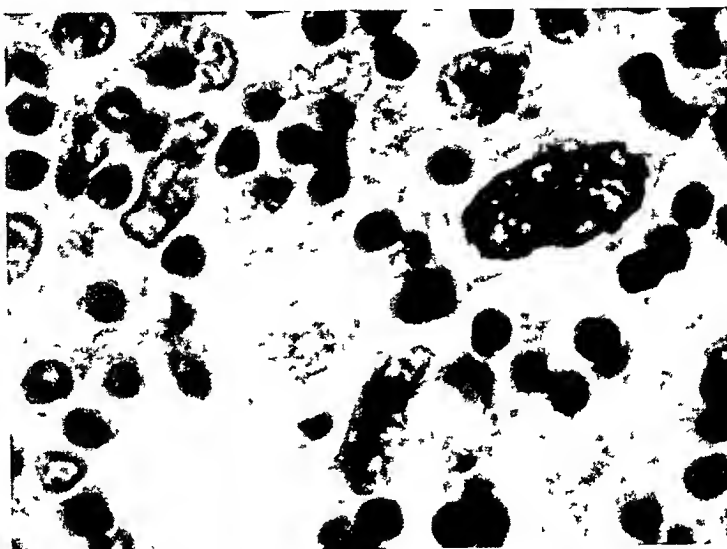


FIG 20 High magnification of tumor shown in two previous figures demonstrating hyperchromatism and macronuclei of the epithelial cells $\times 450$

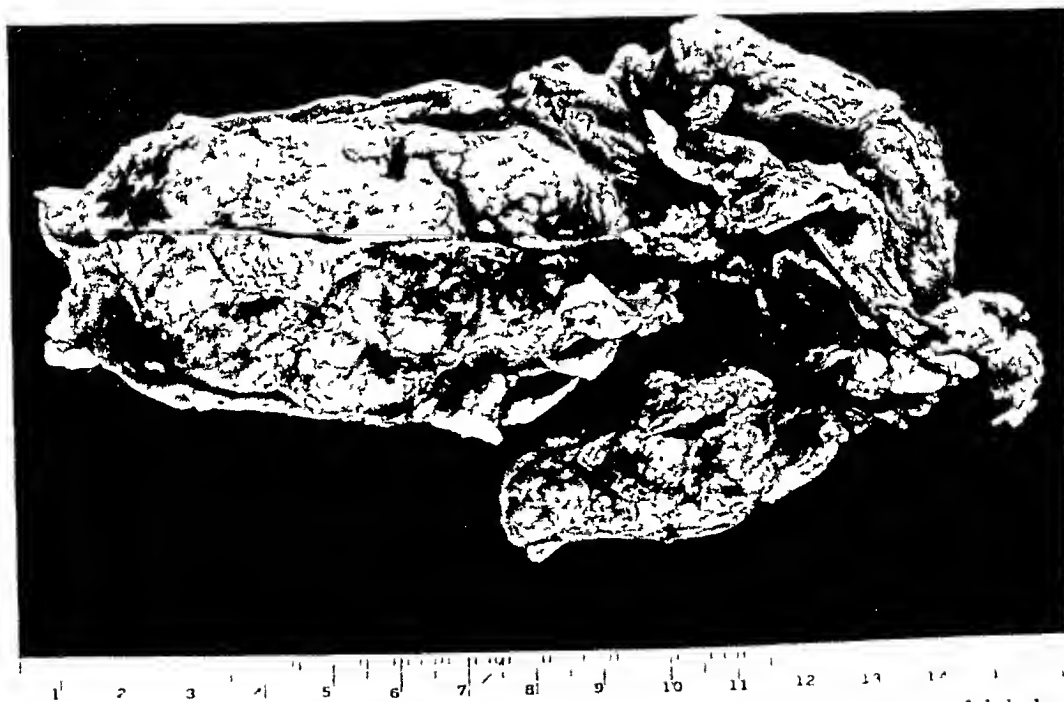


FIG 21 Case 6 Tumor nodule invading diaphragm Note preservation of lobular architecture and reactive blood vessels around tumor $\times 100$

Case 6 (H R , 346,458) A male, thirty-six years old, with symptoms of myasthenia gravis for two and one-half years About eighteen months before death a thymoma was removed The patient improved for a time following the operation, but developed severe dyspnea and died eighteen months postoperatively

Operative findings and gross description of surgical specimen Two lobes of normal appearing thymus were exposed behind the manubrium. In the left lobe a tumor was identified on the lateral aspect of the aorta and upper pericardium. The pleura and lung were adherent to the tumor and a portion of the pleura was removed with the tumor, the tumor was also adherent to the pericardium and the left phrenic nerve, from which structures it could be separated by blunt dissection.

The specimen was a gray white, somewhat lobulated, encapsulated mass that measured $8 \times 6.5 \times 2.5$ cm and weighed 50.5 grams. The cut surface showed relatively soft, grayish pink tissue that was divided into lobules by fibrous septa.

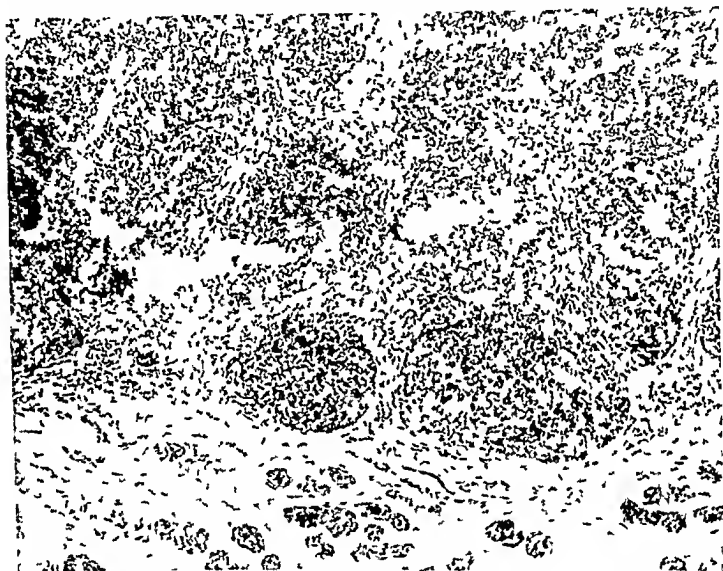


FIG. 22 Case 6. High power view of both epithelial cells and lymphocytes within muscle fibers of diaphragm. $\times 160$

Autopsy findings Mediastinum, thymus, pericardium, and right pleural cavity were negative. The left pleural cavity contained 200 cc of straw colored fluid, when this fluid was removed, a mass $7.5 \times 6.5 \times 1$ cm was discovered adjacent to the left crux of the diaphragm and adherent to the visceral and diaphragmatic pleura. There were no other pleural adhesions.

Microscopic findings The tumor removed at operation was uniformly constituted and had nearly equal amounts of epithelial and lymphocytic tissue (Pattern II). A few Hassall's corpuscles appeared to have been folded into the tumor along with bits of thymic tissue that had been included between expanding lobules of the tumor. No mitoses were found.

The tumor discovered at autopsy on the pleural surface of the left diaphragm had the same basic structure as the tumor removed at operation (fig. 21). It had infiltrated the diaphragm, and muscle fibers in groups and individually were separated and surrounded by tumor tissue in which both epithelial and lymphocytic elements were present (fig. 22).

Within the diaphragmatic lesion there were many more large capillaries and blood vessels than in the mediastinal tumor, these had the appearance of reactive structures rather than essential elements of the tumor

No uninvolved thymic tissue was available for microscopic study

Case 7 (J J , 357,599) A male fifty-seven years of age, whose symptoms of myasthenia gravis began about one year before his death. The patient did poorly on prostigmine and died

Autopsy findings A bilobed mass, having the contours of the thymus, was present in the anterior mediastinum, the right lobe measured $12 \times 4 \times 3$ cm and the left, $5 \times 2 \times 1$ cm (fig 23). The tumor was yellow-gray and had a somewhat lobulated structure. The cut

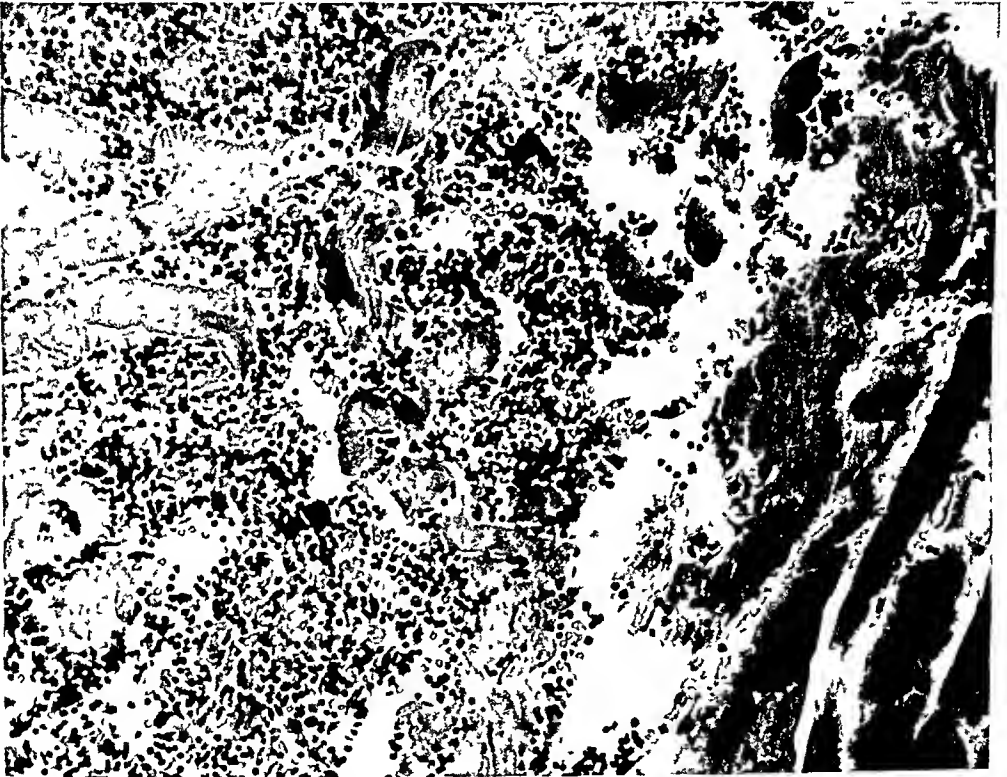


FIG 23 Case 7 Thymoma showing bilobed lobulated structure

surface was divided into lobules of irregular size by strands of connective tissue and some small areas of necrotic softening were noted

Microscopic findings This tumor conformed to Pattern II as there were nearly equal amounts of epithelial and lymphoid tissue. An occasional lobule had a structure more like Pattern III. No Hassall's corpuscles and no mitoses were found within the tumor

No uninvolved thymic tissue was available for microscopic study

Case 8 (J V , 372,501) A male, twenty-eight years old with symptoms of myasthenia gravis for about four years. A tumor in the mediastinum was recognized by x-ray three years prior to the operation. A series of x-ray treatments was given

Operative findings and gross description of surgical specimen A firm, irregular mass was removed from the anterior mediastinum. Normal-appearing, fatty thymus was found near the tumor, but this thymic tissue was not resected. The tumor was a nodular en-

capsulated mass that measured $9 \times 5 \times 4.5$ cm and weighed 97 grams. The sectioned surface was divided by fibrous trabeculae into irregular lobules of soft, friable, pinkish-yellow tissue.

Microscopic findings The greater part of this tumor had undergone necrosis and much of the tissue had been converted into an amorphous mass in which crystals of cholesterol were conspicuous. The structural make up of the viable portions conformed to Pattern II. In its peripheral parts the tumor had a lobular arrangement.

Outside the capsule there were small foci of a few fat cells and an occasional Hassall's corpuscle. A single germinal center was seen in one section.

Case 9 (C K, 26,258) A female, fifty-four years of age, with symptoms of myasthenia gravis for two years preceding her death.

Autopsy findings There was a lobulated, encapsulated mass in the anterior mediastinum that measured $5 \times 4 \times 3$ cm. The cut surface showed grayish pink tissue that was divided into lobules by fibrous trabeculae.

Microscopic findings This tumor had a very uniform structure throughout. It was made up of nearly equal amounts of epithelial and lymphoid tissue (Pattern II). Some areas of liquefactive necrosis were present, but no fat cells, Hassall's corpuscles or mitoses were noted. A thick capsule of dense fibrous tissue surrounded the tumor. Atrophic thymic tissue without any germinal centers was present just outside the capsule of the tumor.

Case 10^a (J S, 237,973) A colored male, forty-eight years old, with symptoms of myasthenia gravis for about nine months.

Autopsy findings In the anterior mediastinum was an encapsulated, ovoid mass that measured $7.5 \times 5.5 \times 2.5$ cm. On section the tissue was gray white, firm and homogeneous.

Microscopic findings This tumor conformed to Pattern III as lymphocytic elements predominated greatly over the epithelial elements. No Hassall's corpuscles, fat cells, or mitoses were seen. There were some areas of necrosis in which cholesterol clefts were prominent. In certain places immediately outside the capsule of the tumor, atrophic thymic tissue with an occasional germinal center was present.

Group B non-neoplastic thymus

Table V gives the pertinent data on the 25 cases that did not have thymomas. Eighteen were operative specimens and 7 were obtained at autopsy. Except for two patients aged forty-six and sixty-two all the patients were under thirty-four years of age. The weights of the thymuses ranged from 11 to 27 grams—all within normal limits for the age of the patient. From the gross examination, one could not detect any difference from a normal gland.

Microscopically, there was one finding that was almost constant and that was the presence of lymphoid germinal centers within the medulla. Because of this striking abnormality the cases were arranged in Table V according to the amount of this germinal center formation. All but the last 6 cases in the table contained some germinal centers and those at the top of the list showed the most extensive involvement.

The description of the first 7 cases in the table may be grouped together. There was only slight involution as shown by the small amount of fat tissue in between the lobules, cortical and medullary zones were readily recognized and seemed to be clearly demarcated from each other in many places. The cortex

^a This case was reported in 1923 by Mella (5).

was composed of islands of lymphocytes with a scattering of a few epithelial cells. These islands appeared denser than normal but this was almost certainly due to the fact that they were compressed by the medulla which contained, and in some areas seemed packed, with lymphoid follicles with germinal centers. This

TABLE V
Non-neoplastic thymus

NO	NAME	SEX	AGE	DURATION OF SYMPTOMS	OP	AUT	THYMUS			
							WT	INVOL	GERM CENTER	COMMENT
				<i>years</i>						
11	D S	F	13	1½	O	—	23	0	++++	
12	M L	F	34	5	O	—	12	+	++++	
13	L M	M	22		O	—	—	+	++++	
14	A S	M	29	3	O	—	15 5	++	++++	
15	A B	F	19	1	O	—	12 6	++	+++	
16	W W	F	29	2	O	—	27	+	+++	L node germ cent +++
17	E H	F	32	11	O	—	11 5	++	+++	
18	V B	F	25	4	—	A	12 5	+	++	L node germ cent ++ Spleen germ cent ++ Parathyroid 2° hyperplasia
19	A L	M	27	1½	—	A	—	+	++	
20	D M	F	24	4	O	—	—	+	++	
21	L R	F	25	4	—	A	—	+	++	
22	H H	M	25	7	O	—	15 5	++	++	
23	M H	F	23		O	—	25	++	++	
24	M P	M	31	1	O	A	—	++	++	L node germ cent 0 Spleen germ cent 0
25	E F	M	34	7	O	—	15 2	++	++	
26	C Z	F	27	1½	—	A	11 3	++	++	L node germ cent + Spleen germ cent + Parathyroid 2° hyperplasia
27	S V	F	19	4	—	A	—	0	+	L node germ cent 0
28	E T	F	21	8	O	—	11 3	+	+	
29	W C	M	30	6	O	—	—	++++	+	L node germ cent +++++ (L node germ cent 0 Spleen germ cent 0 Parathyroid negative
30	C M	F	30	4	—	A	13	+++	0	L node germ cent ++
31	D S	M	19	1	O	—	18	+++	0	
32	E V	F	31	7	O	—	15	+++	0	
33	L T	M	21	2	—	A	23	++	0	
34	F E	M	46	10	O	—	—	++++	0	
35	H H	M	62	2	O	A	—	++++	0	

ballooning out of the medulla produced a pseudo-capsule between the medulla and the cortex. The cortex seemed like a cap over the medulla (figs 24 and 26). This is in sharp contrast to the normal thymus where there is usually a gradual merging of cortex and medulla (fig 27). This capping or sharp separation of cortex from medulla is well brought out with reticulum stains. The latter show

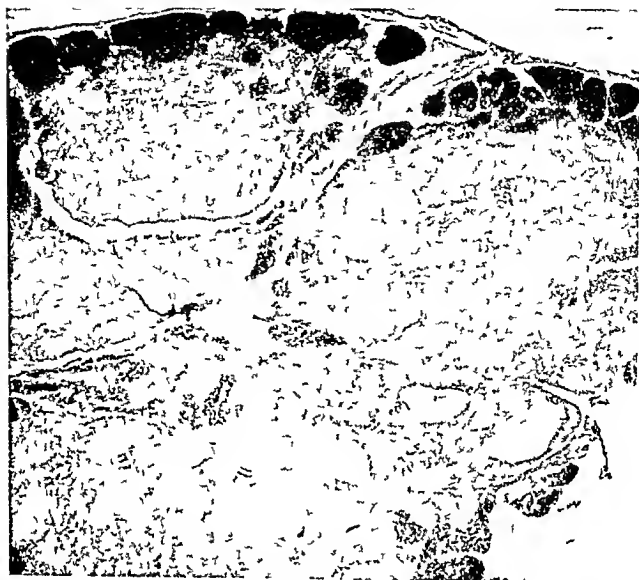


FIG 24 Low power view of non neoplastic thymus in myasthenia gravis showing extensive lymphoid germinal center infiltration of medulla. The cortex appears like a cap around the medulla. $\times 18$



FIG 25 Low power view of moderately involuted thymus in myasthenia gravis showing many germinal centers in medulla. $\times 18$

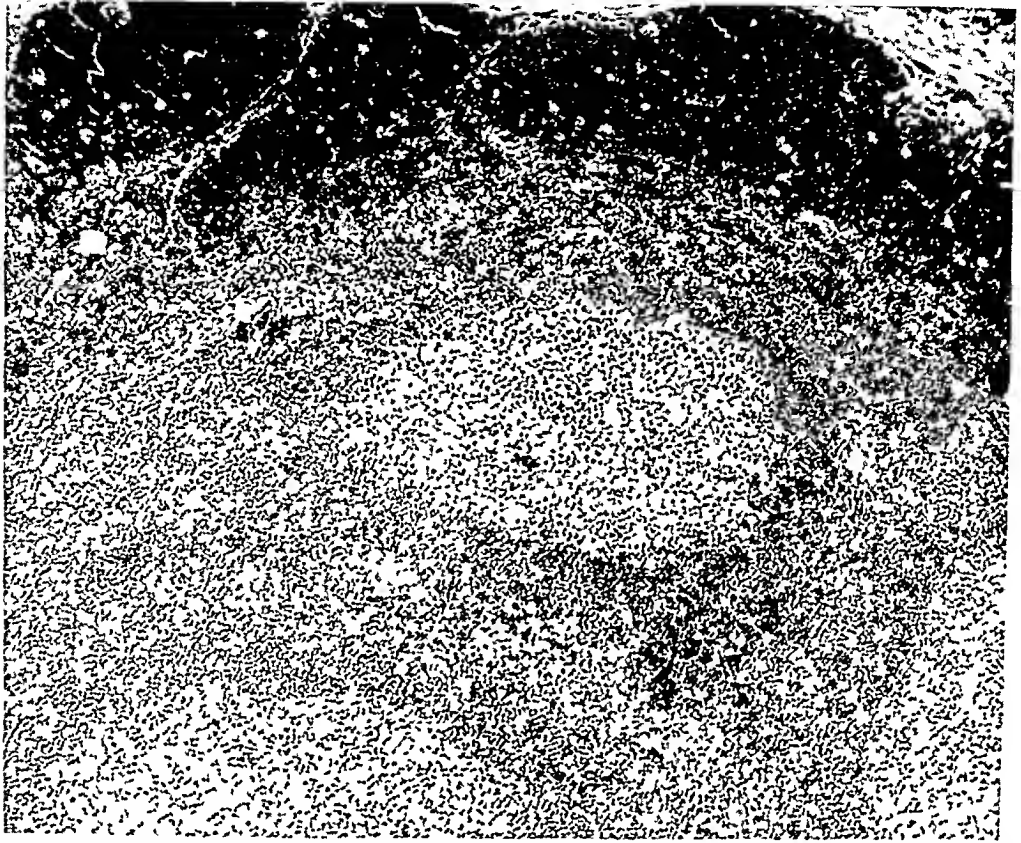


FIG 26 A higher magnification of Figure 24 showing characteristic germinal centers with cuff of lymphocytes $\times 100$

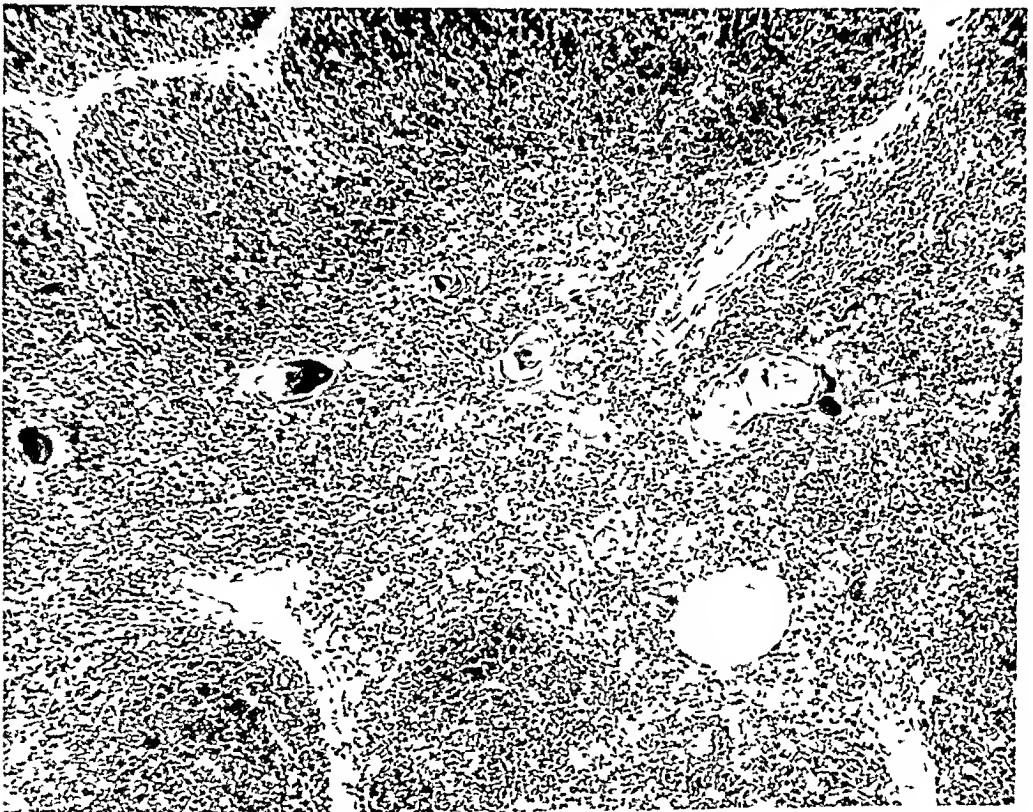


FIG 27 Normal thymus of a boy age eleven showing gradual merging of cortex into

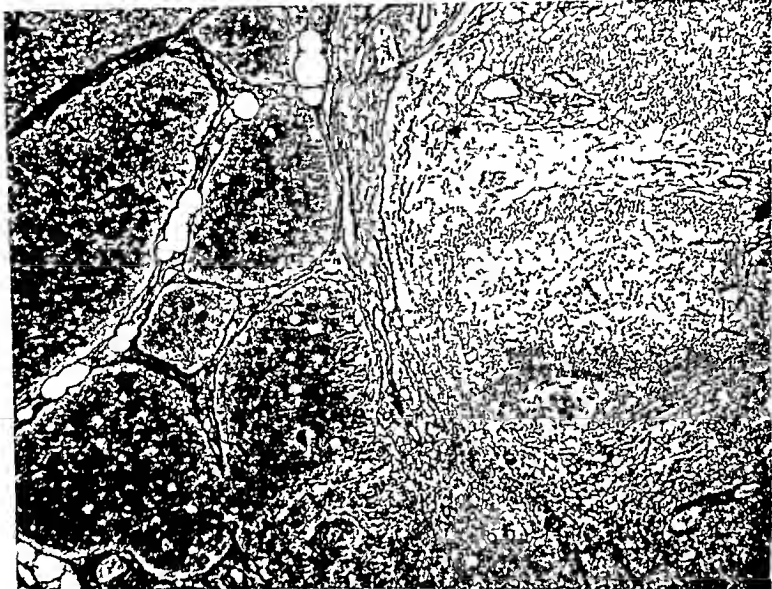


FIG 28 Foote stain of portion of Figure 24 showing reticulum fibers between cortex and medulla Compare with Figure 29 $\times 100$

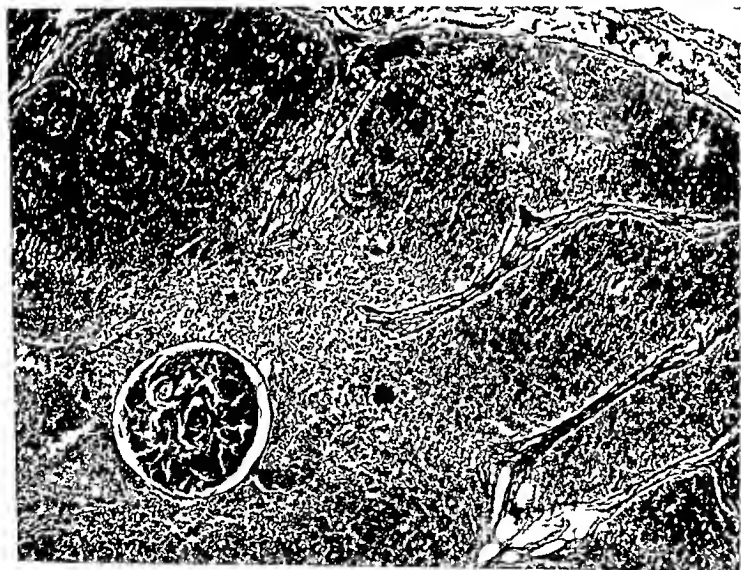


FIG 29 Foote stain of normal thymus (same case as Figure 27) showing absence of reticulum fibers between cortex and medulla $\times 100$

the lymph nodes and medulla in the cases with myasthenia gravis are not in the normal (fig. 28 and 29). The germinal centers were in every respect normal, those seen in lymph nodes—a central zone of immature pale cells with occasional mitoses and a peripheral rim of mature lymphocytes. The latter merged into the normal medulla but there did not seem to be an increase of lymphocytes in the medulla except for those making up the germinal center. The medullary tissue between the follicles appeared normal, containing the normal proportion of lymphocytes, epithelial cells and Hassall's corpuscles. The medullary element here compressed somewhat, but usually there was a fair amount of medulla evident.

The next 3 cases (nos. 18-26) were not unlike the first group except that the number of germinal centers in the medulla were not so numerous (fig. 25). The degree of involution was about the same. Since the medulla was not so distended with a many germinal centers, the separation of cortex from medulla was not too conspicuous.

Of the 3 cases (27-29) with only a rare germinal center, one showed no involution, the second only slight involution, and the last was markedly involuted.

The last group of 6 cases (30-35) contained no germinal centers at all. Of course it is possible that an insufficient number of blocks of tissue were examined to rule out their absence completely. Also the most marked degree of involution had taken place in most of these glands so that there was very little thymic tissue to study. It is interesting to point out that the two oldest patients were in this last group.

Of this group of 25 cases, lymph nodes were available for study in only 8 and germinal centers were present in varying numbers in 5 (Table V). Splenic sections were examined in 4 and only 2 showed an occasional germinal center. An interesting finding was the presence of definite parathyroid hyperplasia in 2 of the 3 cases where this gland was available.

DISCUSSION

Thymoma

Characteristically the thymoma is a firm, irregularly round or ovoid mass that is well encapsulated and whose generally smooth surfaces may be broken by smaller or larger lobulations. The cut surface is divided by septal connective tissue into lobules of irregular size and shape. The parenchyma is soft and grayish-yellow or grayish-pink. Liquefactive cystic areas are frequently noted. Occasionally areas of calcification, particularly in the capsule, have been observed.

The size of the tumor is variable. Rarely, as in our cases 4 and 5, the lesion may fill the mediastinum. It is interesting to note that these patients' symptoms were of three and eleven years' duration—the only two cases in our tumor series with symptoms over three years. The measurements vary but average $7 \times 5 \times 2.5$ cm. Weights have ranged from 10 to 136 grams, with an average of 70 grams.

The thymoma may develop in any part of the thymus as a circumscribed, en-

encapsulated mass. Adjacent to the mass, normal-appearing thymic tissue often forming a rim, has been repeatedly observed. This produces a relationship similar to that caused by the development of adenomas in other glands such as as the thyroid, parathyroid, and pituitary. The structure of the associated uninvolved thymic tissue corresponded rather closely with what would be expected for the age of the particular individual, and in all but one case the rim contained an occasional germinal center.

Judging from post-mortem records, apparently the growth of most thymomas tends to be self-limited at a point of moderate size, this appears to be so, for some cases have been observed by x-ray over years of time. Characteristically, the tumor grows by expansion, and atrophy or displacement of neighboring structures may occur, or such structures as the phrenic nerve may become incorporated by the tumor. Occasionally the tumor may attain a huge size and grow until it nearly fills the mediastinum (Cases 4 and 5).

In general, the gross appearance of thymomas conforms to what might be expected of benign tumors. Although the very large tumors of our cases 4 and 5 had broken through their capsules and there was invasion of the overlying pleura and lung, the extension of these particular tumors did not have the appearance of disorderly, wild invasion, it was more like an orderly expansion with encroachment upon the pleura and the adjacent pulmonary parenchyma. In no case in our series did we observe evidence of distant metastases.

However, as indicated by case 6, apparently a thymoma may grow from a transplant. In case 6 the surgeon had opened the left pleural sac while removing the mediastinal tumor, eighteen months later at autopsy a small tumor, having the identical structure of that previously and completely removed from the mediastinum at operation, was found growing on the pleural surface of the left diaphragm. That this diaphragmatic lesion represents an accidental surgical transplant seems very likely. It is not interpreted as a metastasis because, 1) the primary tumor was not malignant, 2) there were no other metastases, 3) this diaphragmatic lesion was not destructively invasive after the manner of metastases, 4) the opening of the left pleural sac during the operation provided the opportunity for a fragment of the mediastinal tumor to be introduced into the pleural cavity and to settle in the most dependent place, and 5) the diaphragmatic lesion caused the growth of large numbers of new-formed capillaries. These capillaries are like those that would form in response to a mild, chronic irritant.

As indicated in our case 2, the thymoma may develop in ectopic situations. Although at operation and at autopsy no tumor was found in the usual location of the thymus, a tumor having the histologic characteristics of a thymoma was found at autopsy attached to the anterior surface of the left bronchus. The presence of a bit of thymic tissue in this region can be readily explained embryologically. This case is very important because it raises the question as to whether in some of the cases of myasthenia gravis in which only normal-appearing thymus was found either at operation or at autopsy, a thymoma may well have been present in ectopic locations and not discovered. Lobules of thymic tissue are not infrequently found in the neck and any where in the mediastinum. Perhaps

some of the cases that seem to be out of line with respect to age and duration of symptoms might have had undiscovered thymomas. It is difficult to avoid the analogy to the parathyroid tumors which, we know, not infrequently occur ectopically in the mediastinum. It was only the chance autopsy finding of a large parathyroid tumor in the mediastinum that has led to the routine mediastinal explorations for parathyroid adenomas when none is found in the neck.

For simplicity and to aid in comparisons we described three histologic types. Pattern I in which the epithelial elements far outnumber the lymphocytes and whose structure resembles an early embryonic thymus, Pattern II in which the epithelial cells and lymphocytes were present in nearly equal amounts, and Pattern III in which the lymphocytes outnumbered the epithelial cells. For the most part, these tumors tended to have the same pattern throughout, but in some, there were examples of more than one pattern (Table IV). There was no correlation of the structural patterns with the age, duration, and character of the patient's disease. The patterns have emphasized the resemblance of the tumors' architecture to stages in the normal histogenesis of the thymus (6) and account for the single or mixed structural arrangements within the same tumor. Use of these patterns has also provided us with an explanation for the variety of histologic diagnoses that have been attached to this tumor in the literature. This tumor has been called thymoma, malignant thymoma, grade four thymic epithelioma, carcinoma, perithelioma, lymphosarcoma, thymoma, lymphosarcoma type, benign lymphocytic thymoma, etc. Apparently these names have been multiplied because it has not been appreciated that for the same tumor there existed a variety of histologic patterns that corresponded to stages of thymic histogenesis.

The large, poorly-outlined epithelial cell with its large vesicular nucleus is the most characteristic element of this tumor. In examples of Pattern I these cells are arranged in irregular cords or masses. In examples of Patterns II and III the epithelial cells are more widely separated from one another. Mitoses are rarely observed in the epithelial cells. In only the two cases with extensive mediastinal involvement did we observe any considerable variation in the size of epithelial cells. Lymphocytes are present in all thymomas in numbers that are inversely proportional to the number of epithelial cells. The lymphocytes appear to be wedged in between the epithelial cords in Pattern I, and in Patterns II and III they fill the interstices of the epithelial syncytium. Hassall's corpuscles do not form an essential part of the thymoma. It is our opinion that when Hassall's corpuscles are found within the tumor they represent bodies that have chanced to be incorporated by the expanding tumor.

Is the thymoma of myasthenia gravis a true tumor?

Several facts and observations lend support to the thesis that the thymoma is a true neoplasm. In the first place, the lesion develops within the thymus gland and has the form of a circumscribed, expansive, encapsulated mass, and uninvolved thymic tissue is commonly associated with the lesion. If this were merely hyperplasia, one would expect all the thymic tissue to respond in the same

fashion. The rim of normal tissue around the lesion argues in favor of a neoplasm. Secondly, the thymoma grows by expansion after the fashion of other benign growths. Thirdly, as in other tumors, this lesion is made up of tissue in which various stages in the histogenesis of the thymus are simulated. Finally, the fact that thus far we have no evidence that this lesion is physiologically active does not contend against its neoplastic nature. We know so little regarding the function of the thymus that it would be easy to overlook evidence of physiologic activity.

If we therefore admit that the thymic lesion is a true tumor, is it always benign? We have indicated above that although the tumor may grow to fill the mediastinum, may even encroach upon the lung and pericardium, in none of our cases nor in those reported in the literature has there been evidence of a true metastasis. It is true that nodules have been found on the pleura in a few cases reported in the literature but from the evidence in our case 5 where an implant developed postoperatively on the diaphragmatic pleura, it is not unlikely that the pleural nodules in the reported cases are also implants. If implantation connotes malignancy, then the thymoma may be carcinomatous in a very small percentage of cases (between 5-10 per cent). However, even in these cases the cytology is not that of a very malignant tumor. Mitoses, if present, are rare. By and large, the thymoma of myasthenia gravis should be considered as a benign neoplasm.

Non neoplastic thymus

Most authors agree with the observations made by Hammar (7) in 1926 on the weight of the thymus in relation to age. His findings are graphically depicted in Figure 30. Several conclusions regarding the growth and age changes in the normal thymus seem evident. From birth to puberty the thymus increases in size. At or about puberty the thymus attains its maximal size and beginning shortly after puberty it decreases in size rather rapidly. During middle life the thymus continues to decrease in weight but the rate of decrease is less rapid than during the period of young adulthood. Throughout life there is a great difference between the minimum and maximum weights of thymuses from normal individuals of the same age. Although the atrophy of the thymus is very considerable in individuals of advanced years, the gland does not disappear, *normally it persists in an atrophic state*. The examination by Sloan (8) of 350 thymuses, 200 from routine autopsies at the Johns Hopkins Hospital and 150 from patients who died suddenly and were autopsied at the City Morgue, confirmed the well-known facts about the histology and involution of the thymus. Similar findings were obtained by Murray and McDonald (9) from a series of 110 thymuses. Our own general observations of the thymus in routine autopsy material agree with those of Hammar and Sloan.

Remembering the range of individual variability that is normal for the thymus of any age group, it is striking how well the weight of the glands in our series of 25 non-neoplastic thymuses as well as all the nontumor cases reported in the literature corresponds to what would be well within normal limits for the age of the

particular patient (fig 30) Thus it is fair to say that the use of the terms "enlarged" or "persistent" as regards the thymus found in myasthenia gravis is not justified The thymus normally persists and in myasthenia gravis it does not weigh any more than the thymus of persons without myasthenia gravis As Sloan has stated, "The criteria of abnormality are not to be sought in the size of the gland but rather in its microscopic appearance" This microscopic difference, namely, the germinal center formation in the medulla, well described by Sloan, has not been sufficiently emphasized In our series it was present in 75

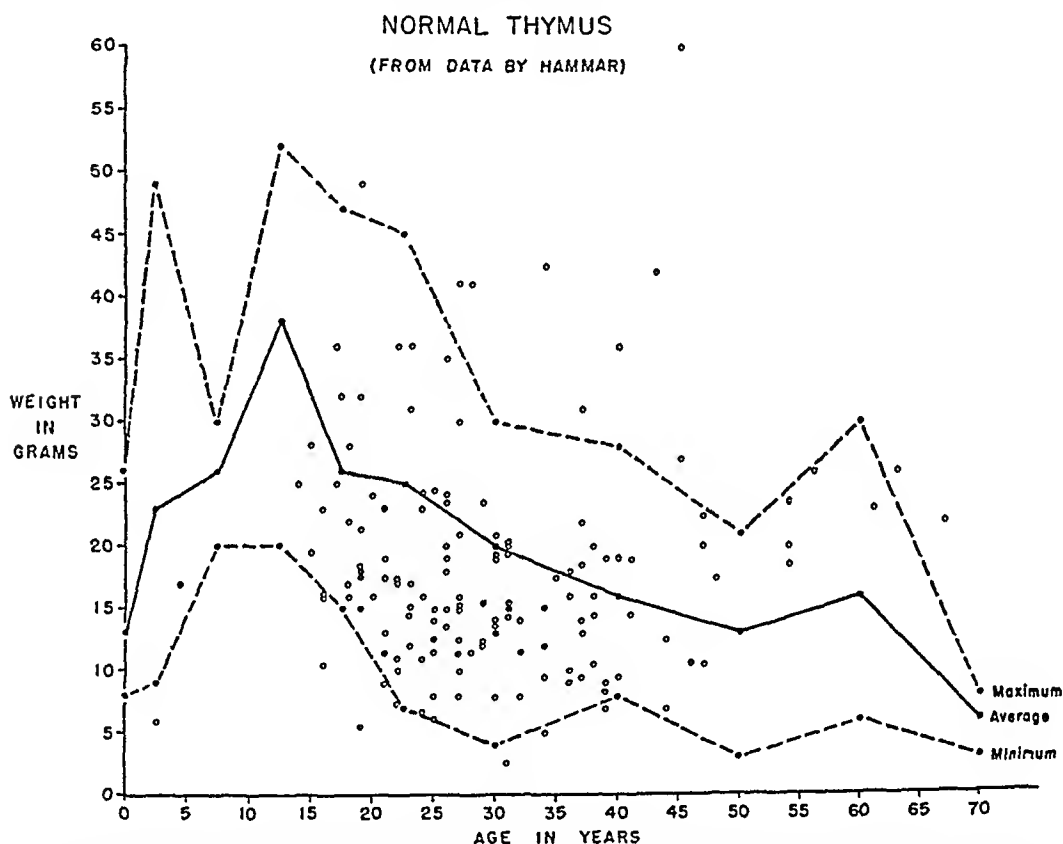


FIG 30 Graph based upon Hammar's figures showing the wide variation of thymic weights at any given age The circles represent the weights of the non-neoplastic thymuses in cases of myasthenia gravis

per cent of the cases Most histologists agree that germinal centers are not observed in the normal thymus Sloan, however, did find an occasional lymphoid follicle in 14 of 150 glands from people who died suddenly without previous chronic disease, but since these were city morgue cases, one cannot be sure of the clinical histories and physical findings We have not observed them in normal glands. Sloan also found a few germinal centers in 5 of 20 patients with hyperthyroidism, in 2 of 5 patients with acromegaly, and in 3 of 7 patients with Addison's disease It is well known that the thymus in hyperthyroidism is prominent, but this may be due to the lack of involution and what one usually finds is merely the childhood type of thymus The large numbers of germinal centers seen in myasthenia gravis are not present in hyperthyroidism and in the small percentage

of the cases where germinal centers are found, they are relatively few in number. The same is apparently true for acromegaly and Addison's disease. In myasthenia gravis, on the other hand, involution of the thymus does occur and the germinal center infiltration seems to develop independently. It is true, however, that the few cases in our series that did not show germinal centers were the markedly involuted glands where there was very little thymic parenchyma present. Perhaps more thorough examination of these glands would have disclosed them. We believe it is fair to conclude that the presence in the thymus of germinal centers in large numbers or in smaller numbers associated with thymic involution almost certainly means myasthenia gravis.

The thymus and myasthenia gravis

The symptoms of myasthenia gravis were described as early as the seventeenth century and the malady was established as a clinical entity in the latter part of the nineteenth century by the descriptions of Wilkes (10), Erb (11), Oppenheim (12), Goldflam (13) and others. Since then, despite the fact that the disease has held the attention of many investigators, little progress seems to have been made in clarifying the fundamental nature of the malady. The discovery of prostigmine as a therapeutic agent, for a time, offered hope that this drug might also become an aid in exploring the nature of the disturbed physiology, however, efforts along this line of investigation have thus far been inconclusive.

From the point of view of the pathologist, myasthenia gravis is still a clinical state for which no regularly associated organic, chemical, or functional changes have been recognized as constants in all cases. The tissues of the central and peripheral nervous systems have yielded no specific lesions. In the skeletal muscles lymphorrhages may be found but their significance is certainly open to interpretation.

Without doubt the changes in the thymus are the most conspicuous and impressive lesions that have thus far been identified with myasthenia gravis. Our studies indicate that the thymoma is found in about 15 per cent of the cases that clinically are called myasthenia gravis, and that this particular tumor probably occurs only in myasthenia gravis. If our conclusion is correct that the thymoma is a true tumor then it is difficult to believe that it is a result of, and secondary to the myasthenia gravis, although the results from the surgical removal of thymomas are apparently not sufficiently dramatic to establish an etiologic relation of the tumor to the disease. Of the 6 cases of thymoma operated upon, one was inoperable, two died postoperatively and one died one and one-half years after operation. The two remaining patients have been followed about one and five years. The former is entirely well and the latter is only slightly improved. Keynes (14) of London operated upon 11 thymomas and removed the tumor in 8 cases. Six died either postoperatively or from a myasthenic crisis later on, and of the remaining two, one is no better, and the other only slightly improved. The Mayo Clinic's report (15) on tumors seems better, a fair result having been obtained in 11 out of 15 operable cases. Of the 3 tumor cases at Johns Hopkins (16), one is apparently cured, one is somewhat better and one died.

On the other hand, if the non-neoplastic thymus with germinal center infiltration which includes the majority of cases of myasthenia gravis is merely a secondary hyperplasia, it is surprising that many of these patients are improved after thymectomy. Since the first large series of thymectomies for the non-neoplastic thymus was reported by Blalock (17) only as recently as 1941, long follow-ups are not yet available. There is no doubt, however, that complete remissions and definite improvements have occurred. At a recent myasthenia gravis conference the results shown in Table VI were reported.

TABLE VI
Results of thymectomy (nontumor cases)

	NO CASES	PERCENTAGE GOOD RESULTS
Keynes	100	50
Mayo Clinic	40	43
Johns Hopkins Hospital	29	45
Mass General Hospital	16	44

TABLE VII
Correlation of percentage of improvement and germinal center formation

AGE	DURATION	GERMINAL CENTER	YEARS POST OPERATIVE	PERCENTAGE IMPROVEMENT
	<i>years</i>			
32	11	+++	6	95
34	5	++++	1	85
34	7	++	6	85
46	10	++++	4	75
19	1	0	5	55
21	8	+	6	50
30	6	+	5	50
29	3	++++	6	25
19	1	+++	4	15

In our series of cases we have not been able to make any definite correlation between the relative incidence of germinal centers and the percentage of improvement following thymectomy. Viets has carefully estimated this percentage of improvement, based primarily on the decrease in the amount of prostigmine that the patient requires. Nine patients of the nonthymoma group have been followed from one to six years and it is interesting that the 4 with 75 per cent or better improvement did belong in the groups with the larger number of germinal centers (Table VII). There were, however, 2 in the upper groups who showed poor results. The 3 patients in the lower groups (0 or + germ center) showed about 50 per cent improvement.

We have not been able to establish any relationship anatomically between the thymoma and the germinal center infiltration. No germinal centers were observed within any of the thymomas, but were seen in the rim of thymus around 6 of the 7 tumors in which a rim of thymus was available. Since the patients

with thymomas by and large have symptoms for shorter periods of time than those without tumors, it is difficult to assume that the germinal center came first and stimulated the development of the thymoma. Also since only a relatively small percentage of the cases of myasthenia gravis have thymomas, the latter could not have stimulated the lymphoid follicle.

Does this germinal center infiltration represent lymphoid hyperplasia? Whether the small cell of the thymus is a thymocyte and different from the lymphocyte has not yet been settled. Most people believe that they are true lymphocytes and perhaps the fact that lymphoid germinal center can develop in the thymus would argue in favor of this theory. If so, this infiltration with lymphocytes does represent lymphoid hyperplasia. Since this type of hyperplasia is so common in lymph nodes and in various organs in association with chronic inflammation, one must assume that this is a secondary non-specific response to some stimulus and one that primarily affects the thymus because in most of the autopsied cases there is no generalized lymphoid hyperplasia. It is apparent that throughout this paper we have not used the term "thymic hyperplasia." This has been done purposely to avoid any inference that there is hyperplasia of the epithelial elements.

It is possible that in the future the entire group of clinical cases that now are called myasthenia gravis should be subdivided. To insure this separation those cases having thymomas would constitute one group. We have already shown that by and large there are differences in the two groups as regards age, sex, and duration of symptoms. Perhaps more detailed clinical and chemical investigations may prove the group with the thymoma to be physiologically different from those cases in which the thymus shows germinal center infiltration.

SUMMARY AND CONCLUSIONS

1 The pathology of the thymus gland in 35 cases of myasthenia gravis has been reported in detail. The cases were easily divided into two groups: a small group of 10 in which all or a portion of the thymus was replaced by a neoplasm, and a larger group in which the thymus was entirely normal as regards size and weight, but which on microscopic examination showed varying degrees of lymphoid germinal center infiltration or reaction.

2 Statistical data compiled from our own cases and from 297 cases collected from the literature demonstrated that the normal thymus is more frequent in the female between the ages of twenty and thirty-five in contrast to the thymoma which is more apt to develop in males between forty and sixty years of age. Symptoms of myasthenia gravis are usually of shorter duration in the patient with the thymoma.

3 The thymic tumor of myasthenia gravis is usually an encapsulated, slowly growing, benign neoplasm, weighing about 70 grams. In about 10 per cent of the cases it may encroach upon neighboring structures and may produce local implants, but it has never been known to truly metastasize or to occur outside of the thoracic cavity. Occasionally it may develop in ectopically placed thymus.

Microscopically the tumors are composed of both epithelial and lymphoid

cells in varying numbers and this variation has led to the multiplicity of names for this lesion. We prefer to use the simple term "thymoma," since no correlation was apparent between the histological pattern and the clinical picture.

4 The non-neoplastic thymus in myasthenia gravis showed varying degrees of involution, and in 75 per cent of the cases the medulla was infiltrated with lymphoid germinal centers. Germinal centers are usually not found in the normal thymus, an occasional germinal center is found in a very small percentage of the thymuses of exophthalmic goiter, Addison's disease and acromegaly, their presence in large numbers almost certainly means myasthenia gravis.

5 Although the changes in the thymus are the most conspicuous and constant anatomic change in the patient with myasthenia gravis, thymectomy or thymomectomy has not produced dramatic clinical improvement.

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THE LANDRY-GUILLAIN-BARRÉ SYNDROME

A CLINICOPATHOLOGIC REPORT OF FIFTY FATAL CASES AND A CRITIQUE OF THE LITERATURE¹

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TABLE OF CONTENTS

I	Introduction	60
II	Review of the literature	61
A	Analysis of Landry's paralysis and the Guillain Barré syndrome	61
1	The report of Landry	61
2	Subsequent early reports	62
3	The criteria as set forth by Guillain	63
4	A comparison of the symptomatology described by Landry and Guillain and Barré	64
5	The significance of the increase in protein in the spinal fluid	64
6	The frequency of increased cell content in the spinal fluid	67
7	Fatal outcome as a point of differentiation	67
8	Sensory disturbance as a distinguishing feature	70
9	Evidence of neuraxial involvement	72
B	Mode of spread	73
C	The form characterized by equal disturbance of motility and sensibility	73
D	The varying terminology of the disorder	73
E	General conclusions based on the literature	75
III	Clinical observations	77
A	Prodromal symptoms	78
B	Mode of onset	78
C	Course	92
D	Sensibility	95
E	Reflexes	97
F	Sphincter involvement	97
G	Meningeal involvement	98
H	Headache	98
I	Temperature, pulse, respiration and blood pressure	98
J	Mental symptoms	99
K	Cranial nerve palsies	99
L	Visual disturbances	100
M	Herpes	100
IV	Laboratory data	100
A	Virus and bacterial studies	100
B	Spinal fluid	100
C	Blood constituents	102
D	Other data	103
V	Review of the literature of pathologic changes in the Landry Guillain Barré syndrome	104
A	Nervous system	104

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² Work was done at the Army Institute of Pathology while acting as Resident Consultant

1. Introduction	104
2. Peripheral nervous system	105
3. Central nervous system	105
4. Leptomeninges	106
5. Comment	106
B. Other tissues	106
VI. Pathologic observations	107
A. Central nervous system and meninges	107
B. Peripheral nervous system	110
1. Spinal nerves	110
2. Sympathetic nerves and ganglia	115
3. Cranial nerves	115
4. Findings in different clinical syndromes	116
C. Other tissues	119
VII. Discussion	123
VIII. Summary and conclusions	129
IX. References	132

I INTRODUCTION

A disorder ostensibly confined to the peripheral nervous system and usually characterized by albuminocytologic dissociation of the spinal fluid, which has been designated by many terms, such as Guillain-Barré syndrome, infective neuronitis, acute infectious polyneuritis, and polyradiculoneuritis, occurred with a fair degree of frequency in the U S Armed Forces during World War II, but the mortality rate was low. In the past few years, especially since Pearl Harbor, the Army Institute of Pathology received 50 fatal cases of the disorder. Thirty-two of these occurred in the United States, 13 in the European and Mediterranean Theaters of Operation, and 5 in the Pacific Area. One of the patients was in the Women's Army Corps, 2 were soldiers in the British Army, 1 was a German prisoner-of-war, 1 a woman civilian, while the remaining 45 were men in the U S Armed Forces. All of the patients were of the white race.³

In reviewing case after case of this group it became apparent that the pathologic changes in the nervous system were relatively constant, being confined, as a rule, to the more proximal part of the peripheral nervous system, whereas the clinical picture varied considerably. The diagnoses made by the medical officers who saw these patients also differed, but, in general, the diagnosis of "Landry's paralysis" was made when the illness was brief and was characterized by rapidly spreading paralysis with minimal sensory symptoms and little or no increase of protein in the spinal fluid, and the diagnosis of "Guillain-Barré syndrome" when the course was slower, the symptoms included pain and facial paralysis, and the spinal fluid protein was considerably increased and the cell count minimal.

In a preliminary analysis of the clinical histories in this series, we were confronted with a number of cases which defied inclusion in one or the other of these categories, as they presented features not in complete accord with either. We

³ In one fatal case which reached the Army Institute of Pathology after this study was completed, the patient was a negro, he was 45 years of age and the duration of his illness was approximately 2 days (AIP Acc 182047). The disorder apparently is rare in the negro race, for only one recorded case could be found (116).

gained the impression that these were transitional cases linking the two syndromes into one, but before this impression could be substantiated it was necessary to reexamine the reports of Landry and Guillain and Barré in order to assess the nature of the differences which are said to exist between the two. In addition to reviewing the pertinent literature on the subject, the purpose of this paper is to describe the clinical and pathologic features of the 50 cases of our series, and to analyze the data in an effort to determine whether or not the many appellations refer to one and the same basic disorder.

II REVIEW OF THE LITERATURE

A Analysis of Landry's Paralysis and the Guillain-Barré Syndrome

1 *The Report of Landry* Landry's original communication in 1859 (120) was based on 10 cases. Five were his own and the other 5 had previously been reported in the literature. One was described in detail.

In this case the patient was a man aged 43 years, a road paver by occupation, who had had several bouts of severe pain in the extremities over a period of 10 months. Tingling sensations in toes and fingers were experienced for one month prior to his fatal illness.

Difficulty in walking was the first manifestation of the final illness. On the next day a tingling sensation developed in the feet and hands, and within a few hours spread upward to the thighs and arms. Motor power was increasingly affected, so that by the fourth day the patient could neither stand nor walk, nor, when in a dorsal recumbent position, could he lift his legs or turn to a lateral position, although he still retained trunk movements. He could not raise his arms to the horizontal plane, but he could still make use of his fingers and hands. No deep or superficial reflexes could be elicited. By the sixth day the paralysis had spread, and there was tingling around the thorax and at the base of the neck and he was having difficulty in respiration. On the seventh, all the extremities were paralyzed, movement of the ribs was greatly restricted, and difficulty in respiration, mastication, deglutition, and speaking had developed.

On the eighth day the paralysis of the legs was found to be most marked in the muscles innervated by the sciatic, in the arms the paralysis was virtually complete except for the deltoid and the flexors and extensors at the left elbow, which retained a little of their power. The trunk and deep cervical and intercostal muscles were almost completely paralyzed. During inspiration the thorax was raised chiefly by the trapezius and sternomastoid muscles, and evidence indicated that the diaphragm was paralyzed. The abdominal muscles contracted voluntarily, though somewhat feebly. At this time paralysis of the tongue was almost complete and there was tingling of the cheeks. The facial muscles were spared. The pulse rate was 85 to 90 per minute. (The cranial nerves affected, therefore, were the Vth, IXth, Xth and XIIth.) Urinary and fecal incontinence had set in. Thermal and pain sensibility were not altered, but there was anesthesia of the feet and fingers, and hypesthesia of the medial aspect of the legs and forearms and of the posterior and lateral aspects of the trunk. Appreciation of movement of the toes and fingers also was lost. Death occurred suddenly on the eighth day after the onset of motor weakness.

The mental state was unaffected throughout the course of the illness. At no time was headache or pain in the body or limbs experienced. The temperature remained normal except for an occasional slight rise. The spinal fluid was not examined. At autopsy no lesions were observed, except lobular pneumonia and traces of pleurisy. The peripheral nerves were not examined.

In his discussion, Landry summed up the progression of the disorder as follows. The paralysis may be preceded by a feeling of fatigue, tingling, and, at

times, transitory cramps The first phenomena are always manifested at the distal parts of the limbs, most frequently in the lower Subsequently, the following are affected 1) muscles of the toes and feet, the posterior muscles of the thighs and pelvis, and finally the anterior and medial muscles of the thigh, 2) muscles of the fingers, hands, arm and shoulder, later the muscles of the forearm, 3) muscles of the trunk, 4) respiratory muscles, tongue, pharynx, esophagus, etc Usually the paralysis spreads rapidly from the lower limbs to the upper, with a constant tendency to "generalization" Should the paralysis retrogress, the phenomena are inverse to those of the progression period, recovery starting in the upper parts, which were involved last, and proceeding downward Death may occur in a few hours or in 2 or 3 days Of the 10 cases described in this article only 2 were fatal As to sensory symptoms, Landry stated that they are usually minimal but that sensibility and motility may be equally involved "Dans l'espèce de paralysie sur laquelle je désire appeler l'attention, la sensibilité et la motilité peuvent être également compromises" The propagation of the paralysis was "extenso-progressive" it began in a relatively small area of the body and then spread either in a seemingly organized manner, i e, by contiguity, taking an ascending (centripetal) course, or it became generalized without systematized sequence

It is apparent, then, that Landry described 3 forms of the disorder, *one* that first affects the nerves of the limbs, producing both motor and sensory symptoms, especially the former, then involves the trunk, cranial and intercostal nerves (i e, becoming "generalized without systematized sequence"), a *second* which ascends the neuraxis or affects successively higher neuraxial nerves, with almost sole involvement of the motor neurons (i e, advancing in "systematized sequence"), and a *third*, of the same character as the second except that motility and sensibility are equally affected

2 *Subsequent Early Reports* The importance of Landry's report went unrecognized until 1865, when Pellegrino-Lévi (154) referred to it and emphasized that the disorder may begin in the domain of cranial nerves and descend, and cited as an outstanding example the case of Cuvier, who died in 1832 Bernhard's paper in 1871 (19) on "acute generalized paralysis" dealt with a case of 10 days' duration in which weakness developed simultaneously in the upper and lower extremities, and in which pain occurred in the latter part of the course Case after case of progressive paralysis accompanied by sensory symptoms then appeared in the literature Among the first was that of Eisenlohr (1874) (65), who expressed the opinion that such cases belonged in the same category as those described by Landry In this connection, Westphal (223) related in 1876 the history of a fatal case in which the disorder was ushered in by widespread severe pains, and Vulpian (216), in 1879, drew attention to instances in which objective changes in sensibility were pronounced, as did Kahler and Pick (114) in 1880; Westphal was the first to use the term "Landry's ascending paralysis", though this distinction is usually accorded to Vulpian An illuminating account of the features of the disorder was presented by Dejerine (50) in his Thèse de Paris in 1879 Leyden (125), in an important contribution in 1880, clearly distinguished Landry's ascending paralysis from anterior poliomyelitis

Accounts of the disorder multiplied in the early part of the 20th Century, and during World War I the significant report of Guillain, Barré and Strohl (97) appeared. It concerned the nonfatal illnesses of 2 French soldiers whose symptoms were similar in many respects to those described by previous writers, and doubtless the report would have been relegated to the commonplace had not the authors examined the spinal fluid and found a great excess of protein without increase in cells (albuminocytologic dissociation). It was because of the spinal fluid findings that the cases attracted widespread attention. In 1925, Guillain, Alajouanine and Périssou (95) published an account of 2 more cases, which differed in no essential from those just referred to. The first to use the term "Guillain-Barré syndrome" were Draganescu and Claudian (58), in 1927, but the reason for not similarly recognizing Strohl's part in the original report is not evident.

3 *The Criteria as Set Forth by Guillain* In a publication in 1936, which dealt with 10 more nonfatal cases characterized by albuminocytologic dissociation, Guillain (93) listed what he regarded as the main features of the disorder: 1) an onset characterized either by paralytic phenomena or paraesthesias and/or pain, or all three, with or without premonitory symptoms such as sore throat, malaise, digestive disturbances, and stiffness of muscles, 2) motor disturbances leading to flaccid paralysis of the muscles of the lower limbs and later the trunk and upper limbs, the paralysis affecting chiefly the distal muscles of the limbs "as in polyeuritis" (but if one undertakes to analyze Guillain's 10 cases it is apparent that distal muscles were electively involved in only 4, that proximal muscles were chiefly affected in 3, and that in the remaining 3 the paralysis was too general to permit a statement as to the site of initial involvement), 3) fibrillary twitching, occasionally, 4) slight atrophy of distal muscles, occasionally, 5) ataxia in a moderate number (4 of the 10), 6) abolition of tendon reflexes in the domain of the paralyzed muscles and sometimes beyond, and usually a preservation of the superficial reflexes, though as the disorder progresses they may be lost, 7) subjective sensory disturbances, such as pain, cramps, formication and numbness, 8) rather minor, infrequent, and transitory objective changes in sensibility, both cutaneous and deep, especially at the periphery of the limbs, and pain on application of pressure to muscles or to nerve trunks, 9) astereognosis, occasionally, 10) difficulty and slowness in micturition and loss of perception of the passage of urine in a few cases, and sphincter disturbances in even fewer, 11) transient palsy of cranial nerves, notably the VIIth, and occasionally the extraocular nerves, the Vth, the IXth, and Xth, and the XIIth, sometimes leading to fleeting disturbances of phonation, swallowing, respiration, and cardiac rhythm.

The cases of Guillain included some in which only the limbs were affected. Guillain and Kreis (98), van Bogaert and Maere (206), and others before them described instances in which only cranial nerves were implicated, thus constituting, from a topographic standpoint, 3 forms of the disorder: that affecting limbs solely, that affecting structures supplied by cranial nerves solely, and mixed. Subsequently, Guillain (94) suggested a fourth category, in which were included the cases with severe mental symptoms.

4 *A Comparison of the Symptomatology Described by Landry and by Guillain*

A comparison of the symptomatology of the form of Landry's paralysis "without systematized sequence of paralysis" (type 1 referred to in the foregoing) and that described by Guillain, point by point, yields the following. As to prodromal symptoms, no essential differences exist. Mild fever was noted in one of Landry's cases and in Guillain's case No. 6. The paralysis was flaccid, began relatively abruptly and usually predominated over sensory disturbances in both, it began either in the lower or upper limbs, then affected the trunk and the domain of the cranial nerves. In each there was a tendency to progressive generalization of the paralysis, the only essential difference between the two being that the trunk and intercostal muscles were more frequently and severely involved in Landry's cases. In Guillain's series the paralysis began sometimes in proximal muscles of the extremities, sometimes in distal muscles, and in some instances was so widespread that the starting point could not be determined, in Landry's cases the initial site of involvement was said to have been in distal muscles, but there is no clear account of this in the instance he recounts in detail. Facial paralysis did not occur in Landry's cases and was absent in some of those of Guillain. Aside from the facial nerve, the incidence of cranial nerve involvement was much the same in the cases described by Landry and by Guillain.

5 *The Significance of the Increase in Protein in the Spinal Fluid* A feature on which great emphasis was placed by Guillain was the albuminocytologic dissociation of the spinal fluid. This was not a new observation, Roemheld (170) having described it in connection with diphtheritic polyneuritis in 1908, and Feer (68) in 1910, Queckenstedt (166), in 1917, made the same observation in 10 cases of diphtheria and in 3 cases of polyneuritis of undetermined etiology. Guillain insisted that cases belong in the category he described only if the spinal fluid protein is 300 mg per cent or higher (usually 1000 to 2000 mg per cent), but there are many reported instances of the same clinical syndrome in which spinal fluid protein was normal or only slightly elevated—Forster, Brown and Merritt's (72) series of 26 cases, for instance, in which the protein content was below 75 mg per cent in 10. Were Guillain's criteria strictly adhered to, one would be obliged to remove from consideration many cases in the literature designated by the term "Guillain-Barré syndrome."

So far as we are aware, Guillain did not state at what stage of the disorder the increase in protein first became evident. It has been amply demonstrated by others that the spinal fluid protein content may vary depending on the stage of the disorder. Thus, the protein value may be low initially, only to rise subsequently to abnormally high levels (57, 75, 79, 107, 108, 128, 173, 195, 207). The curves of 12 such cases are illustrated in figure 1. Had only one protein determination been done in these cases they could not have qualified for inclusion in the Guillain-Barré syndrome, even so, there was only one in which the protein was sufficiently elevated to be regarded as an instance of the Guillain-Barré syndrome in *sensu strictu*. In this connection the remark of Baker (10) is of interest. "We have observed in many of our cases a normal fluid at the onset of the illness only to have the protein become elevated in the course of the disease."

Likewise, Van Bogaert et al (207) have stated " l'hyperalbuminose dans le type Guillain et Barré peut s'installer avec un certain délai " According to Lassen and Fog (122), spinal fluid protein usually begins to rise about the eighth day after the onset of the illness, but this has not been the experience of others

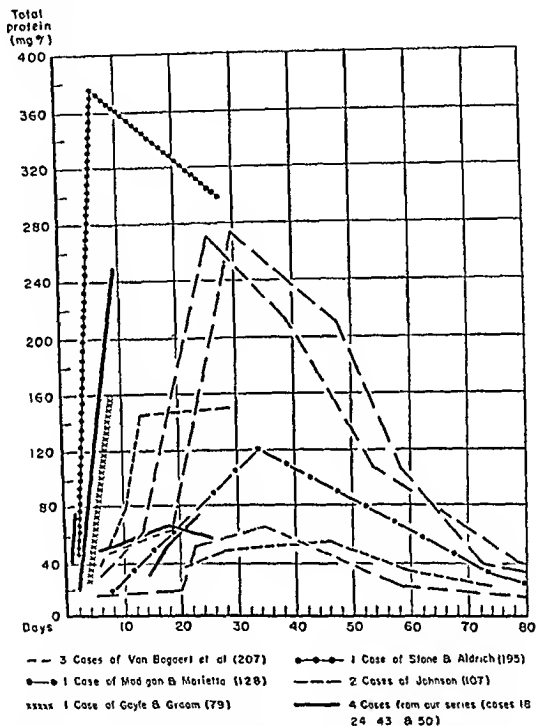


FIG 1 SPINAL FLUID TOTAL PROTEIN VALUES IN 12 CASES OF THE LANDRY-GUILLAIN-BARRÉ SYNDROME

In all of them the initial values were in the realm of normal, and subsequent values were elevated to varying degrees. Eight of the cases were taken from the literature and 4 of them are from our series (AIP Neg 102182)

Certain writers have reported instances of "Landry's paralysis" in which the spinal fluid showed a considerable increase in protein. In Garvey and Slavin's (77) patient, for example, in which death occurred after an illness of 8 days, the spinal fluid protein on the fourth day was 75 mg per cent, and on the seventh day, 250 mg per cent. The opposite condition prevailed in the case of a 14-year old girl reported by Collier (43) the spinal fluid protein was considerably increased (200 mg per cent) and contained no cells when paralysis first affected

the limbs, but later, as her symptoms were subsiding, a relapse occurred, and shortly before death the spinal fluid protein was found to have fallen to 60 mg per cent

It is important to inquire into the cause of this increase in spinal fluid protein which is held in certain quarters to be so essential to the establishment of the diagnosis of the Guillain-Barré syndrome. The explanation given by Govaerts (88), and amplified somewhat by Dagnelie (48), is as follows. Normally about four-fifths of the cerebrospinal fluid escapes into the intracranial venous sinuses by way of the arachnoidal villi, and the remaining one-fifth descends into the spinal subarachnoid space from which it escapes along the radicular sheaths. When an obstruction exists at the level of the radicular sheaths, the amount of fluid descending into the spinal subarachnoid space is reduced and that already present becomes stagnant, if, in addition, the meningeal capillaries are dilated, from whatever cause, plasma protein passes through them to accumulate in the spinal fluid. Govaerts and Dagnelie expressed the opinion that both factors operate in the Guillain-Barré syndrome, the obstruction at the radicular level being caused by tumefaction of the roots in consequence of vascular congestion and edema, and the increase in protein by the passage of an exudate through the walls of dilated radicular and spinal leptomeningeal vessels at the level of the affected roots⁴. According to them the mechanism of production of hyperalbuminosis of the spinal fluid is no different than in other neuritides, the incidence of protein accumulation varying in relation to the degree of involvement of the spinal roots. By injecting thorotrast into the lumbar sac in a case of Guillain-Barré syndrome, Biemond (20) demonstrated radicular obstruction. Guillain (93), however, continued to hold to his opinion that the increase of fluid protein was due solely to exudation through paralyzed leptomeningeal vessels, and was not the result of radicular block, a view in which Barré (12) concurred. According to Greenfield and Carmichael (90), the hyperalbuminosis of the spinal fluid may be ascribed in part to the flow of protein-laden lymph from inflamed nerves into the spinal fluid, an opinion predicated in part on the still unproven view that normally the lymph flow in nerves is toward the cord. That obstruction of the radicular pathways of exit of spinal fluid may be a factor in the collection of protein in the spinal fluid in the Guillain-Barré syndrome is suggested by the edema and vascular congestion frequently noted at autopsy in the roots and the proximal spinal nerves at the region of their passage through the narrow intervertebral canals (48, 88, 181), even though from the standpoint of spinal fluid dynamics, spinal block can rarely be demonstrated.

The observation that the protein of the cisternal fluid is normal or only slightly increased in cases in which the protein of the lumbar spinal fluid is greatly elevated indicates that local factors are most important in the development of hyperalbuminosis. Aring (7) pointed to 3 cases in which this was true. In the first the lumbar fluid contained 330 mg per cent of protein and the cisternal

⁴ As early as 1917, Axel Neel, in demonstrating a case of polyradiculoneuritis before the Danish Neurological Society, remarked that the considerable increase in protein in the spinal fluid might be attributable to a compression of the veins accompanying the nerve roots (cited by Lassen and Fog [122]).

fluid 11 mg per cent, in the second the protein in the lumbar fluid measured 380 mg per cent and that in the cisternal fluid 88 mg per cent, and in the third the protein values were approximately 1400 and 82 mg respectively. Taylor and McDonald (200) also reported a case showing this difference, the lumbar fluid containing 206 mg per cent of protein, and the cisternal fluid four days later 49 mg per cent. In Bassoe's (17) case, in which spinal block existed, the lumbar fluid contained 2000 mg per cent of protein and the cisternal fluid 25 mg per cent. And, finally, in a case described by Peters and Scheid (155) the protein in the cisternal fluid was one-tenth of that in the lumbar fluid.

There are, then, probably two variables on which the amount of protein in the spinal fluid depends. Should tumefaction of the roots be relatively negligible so that excess protein-laden spinal fluid readily escapes from the subarachnoid space, or should the exudation of protein into the spinal fluid be relatively minor, the amount of protein in the spinal fluid obviously may be less than that specified by Guillain and Barré.

From a review of the literature it seems evident that a great excess of spinal fluid protein is not essential to the diagnosis of the disorder brought into such sharp focus by Guillain and Barré.

6 *The Frequency of Increased Cell Content in the Spinal Fluid* Another criterion on which Guillain (93) was adamant was absence of cell increase in the spinal fluid. He stated in 1936 "I refuse to recognize radiculoneuritis with hyperlymphocytosis or hypernucleosis as belonging to this syndrome." A few others have followed suit, believing that the disorder described by Guillain and Barré was due to virus incapable of eliciting an inflammatory response. Among them was Černáček (38) who admitted, however, that variations in cell content might reflect different stages of the same disorder and that definitive distinction between polyradiculoneuritis with and without pleocytosis is not possible as long as the causative agent or agents remain unknown.

Many authors have felt that the paucity of cells has been overstressed as a criterion of the disorder, and that, although the cells are usually within the limits of normal, their number may be considerably increased and may fluctuate during the illness. Clinical evidence of meningeal involvement is so frequently observed—to the extent that some authors have referred to the disorder as meningoradiculoneuritis—that it would be surprising if mild to moderate pleocytosis were not sometimes encountered. Pleocytosis in cases falling clinically in the realm of the disorder under discussion has frequently been reported (table 1). Biernond (20), 3 of whose cases are listed in table 1, has described 1 which he regarded as meningoradiculitis at the onset of the illness and as meningomyelitis later in the course following alleged extension of the disorder into the spinal cord, the cells in the spinal fluid increased (50 to 97 per c mm) and the protein decreased (215 to 145 mg per cent). As a rule, an initial pleocytosis usually falls considerably, sometimes to normal, in a relatively short time. Numerous authors now concur with the remark of Muscio-Fourmer et al (142) that "l'intense lymphocytose du liquide céphalo-rachidien n'exclut pas non plus le syndrom de Guillain et Barré."

7 *Fatality Outcome as a Point of Differentiation* At first glance it would appear

TABLE 1

*Instances of Landry-Guillain-Barré Syndrome in which pleocytosis was observed.
All cases were nonfatal*

AUTHORS	DIAGNOSIS	CELLS	TOTAL PROTEIN OR PANDY REACTION	APPROX DAY TEST DONE AFTER ONSET	STIFF NECK AND/OR KERNIG
		<i>mm³</i>	<i>mgm per 100 ml</i>		
Baker (10)	Encephalo-myelo-radiculitis	154	118	12	—
		1	53	—	—
Biernond (20)	La maladie de Guillain-Barré	63	220	—	—
Biernond (20)	La maladie de Guillain-Barré	34	100	—	—
Biernond (20)	La maladie de Guillain-Barré	70	410	1	—
		50	215	48	—
		86	310	112	—
		97	145	171	—
		12	100	255	—
Chusid & Marquardt (40)	Acute infectious polyneuritis	38	83	4	—
		5	125	29	—
Dagnelie (48)	Polyradiculonévrites avec dissociation albuminocyto- logique	32	800	15	+
		4	400	35	—
De Jong (53)	Guillain-Barré syndrome	33	268	17	+
		4	100	36	—
Fényes & Gottche (69)	Guillain-Barré syndrome	225	4+	60	+
		3	4+	65	—
		8	4+	76	—
		8	1+	390	—
Galpin, Moersch & Kern- chan (82)	Polyneuritis, neuromitis	80	100	—	—
Giraud & Boudouresques (83)	Syndrome de Guillain et Barré	44	1100	5	0
		16	600	7	0
		1	1200	33	0
Krebs & David (117)	Polynévrites	95	1000	163	—
		25	1600	193	—
Merritt & Fremont-Smith (138)	Polyneuritis of unknown etiology	17	648	4/28	—
		175	588	5/18	—
		2	750	11/25	—
		0	492	12/31	—

TABLE 1—*Continued*

AUTHORS	DIAGNOSIS	CELLS	TOTAL PROTEIN OR PANDY REACTION	APPROX DAY TEST DONE AFTER ONSET	STIFF NECK AND/OR KERNIG
		mm	mgm per 100 ml		
Mussio Fournier et al (142)	Méningo radiculo névrite aiguë curable	150	6000	47	+
		514	6500	101	
		30	7500	140	
		24	1080	181	
Polan & Baker (162)	Encephalo myelo radiculitis	57	58	42	+
Riser & Planques (168)	Lcs polyradiculo névrites aiguë	200	1400	—	0
Taylor & McDonald (200)	Polyneuritis with facial diplegia	169	708	70	—
Van Bogaert et al (207)	Poly radiculo névrites avec dissociation albuminocyto logique	51	650	7	—
Van Bogaert et al (207)	Poly radiculo névrites avec dissociation albuminocyto logique	72	450	3	+
von Sánta (213)	Polyradiculoneuritis acuta curabilis	53	3+	10	—
Walter (219)	Polyneuritis	180	1+	37	0
Walter (219)	Polyneuritis	92	2+	5	0

that the most striking difference between the cases of Landry and those of Guillain is that of fatal outcome in the former and benignity in the latter. Reservations should, however, be made. Eight of the 10 cases described by Landry were nonfatal. To be sure, all the cases reported by Guillain and his associates were nonfatal, although in 1 (case 12) of Guillain's (93) there was tachycardia and dysphagia, which temporarily made the outlook grave. In all of his earlier publications on the subject, Guillain insisted that the disorder is nonfatal and therefore does not belong in the same category as fatal Landry's paralysis. In 1932, Barré (14) stated that in the earlier course of the disorder one may tell the patient that he is going to get worse, that he may in fact become seriously ill, that respiratory embarrassment may bring him to the very brink of death, but that he will recover completely.

In 1936, Guillain and Barré (96) appeared before the *Société de Neurologie de Paris* to take issue with those who had published cases under the designation

Guillain-Barré syndrome in which essential features, as defined by them, were lacking. The authors who were the particular object of their attack were Alajouanine et al (5), who had reported a case closely paralleling their own except that death had occurred. Guillain and Barré refused to accept this as an authentic example of their syndrome because of the fatal outcome, and advanced the diagnosis of a polyneuritic type of Landry's paralysis. They attempted to defend their position by stating that they refused to allow their syndrome to become engulfed in that "vast motley which comprised Landry's paralysis," and that they could see no justification for assuming that the causative virus in Alajouanine's and their cases was the same. Alajouanine, answering them in his discussion, argued that a fatal or nonfatal outcome was not a sufficient difference if the course of the disease was similar, typhoid fever, he added, is the same whether it terminates in death or in recovery. Much the same argument was advanced by Dagnehe (48). He could see nothing defensible in Guillain and Barré's stand that the curable form of the syndrome is due to one virus and the fatal form to another.

But in 1938, in a symposium on the subject in Brussels, Guillain (94) stated that the disorder described by him might be fatal, a concession which seems to have escaped the notice of most subsequent workers on the subject. During this meeting, Van Bogaert et al (207) remarked, "Il n'y a d'ailleurs, quand on assiste a la gravité de l'attente bulbaire dans certains cas, aucune raison pour refuser d'admettre l'éventualité, fût-elle rarement réalisée, d'une évolution fatale." In his discussion of such cases, Guillain said, "J'accepte très bien qu'une polyradiculo-névrite avec dissociation albumino-cytologique, présentant une localisation sur les nerfs bulbaires de la respiration et de la circulation, puisse avoir une évolution mortelle," and he likened the Guillain-Barré syndrome to chickenpox, which has a favorable prognosis but occasionally is fatal. The same view was expressed by Barré (12). Thus, another barrier which has been said to separate Landry's paralysis from the Guillain-Barré syndrome was removed.

The question now resolves itself into the frequency with which fatality occurs in the disorder often referred to as the Guillain-Barré syndrome. A mortality rate of 67 per cent was observed in the 15 cases of Lassen and Fog (122), 42 per cent in the 26 cases of Forster, Brown and Merritt (72), 26.6 per cent in the 30 cases of Bradford, Bashford and Wilson (25), 18.8 per cent in the 16 cases of Roseman and Aring (173), 16.6 per cent in the 12 cases of Gordon Holmes (103), 14 per cent in the 35 cases of Gilpin, Moersch and Kernohan (82), and 9.1 per cent in the 33 cases of Baker (10). Analyzing a series of 126 cases reported in the literature, Fox and O'Connor (73) noted a death rate of 20.6 per cent, which is almost precisely the same as in Landry's 10 cases, namely, 20 per cent.

8 *Sensory Disturbances as a Distinguishing Feature.* Great stress has been laid by some authors on the occurrence of pain, aching, and tenderness of nerve trunks and muscles as a criterion for distinguishing the two, Landry's paralysis being allegedly unattended by neuritic symptoms, and the Guillain-Barré syndrome characterized by them. In the case Landry (120) reported in detail, bouts of pain or transitory cramps occurred prior to the onset of the disorder,

and there were paresthesias and reduction in sensibility during its course. In characterizing the entire series of 10 cases, he stated that spontaneous radicular pain and pressure-pain were absent, but added that disturbances of sensibility were sometimes as severe as those of motility. As in Landry's paralysis, pain was lacking in some cases of the Guillain-Barré syndrome: thus, in 4 of Guillain's 10 cases neither pain nor aching was reported, and in 1 (case 6) neither pain nor aching nor tenderness of nerve trunks or muscles (93). It is apparent, then, that Landry's and Guillain's own words refute the view that Landry's paralysis is strictly a motor disorder and that the Guillain-Barré syndrome must necessarily be characterized by pain or other outspoken sensory disturbances.

The question of the significance of sensory symptoms in ascending paralysis led Osler (146), in comparing acute febrile polyneuritis with Landry's paralysis in an early edition of his *Principles and Practice of Medicine* (1892), to state that "diagnosis is difficult" and if we include in Landry's paralysis the cases in which sensation is involved, distinction between the two affections is impossible," and he went on elsewhere in his text-book to say, "The clinical picture of acute febrile polyneuritis is not to be distinguished, in many cases, from Landry's paralysis." In going on the assumption that these were two different conditions, Osler was endorsing what Hun (104) had contended the previous year (see also Bailey and Ewing [9]), but his indorsement was obviously half-hearted. Gordon Holmes (103) followed Osler's lead in his account of "acute febrile polyneuritis" as seen in World War I, when he wrote "Certain of the cases I had seen had been diagnosed as Landry's paralysis, and the separation of polyneuritis from this is not easy, owing chiefly to the vague and indefinite conception of the disease that characterizes its description in many textbooks. But it now is generally accepted that this term [Landry's paralysis] should be restricted to a condition which begins with a progressive paralysis of the lower limbs that rapidly ascends and involves the trunk muscles, later those of the arms, and as a rule leads to a fatal termination from respiratory palsy before the cranial nerves are affected. Objective sensory disturbances are also very slight or absent and the sphincters are rarely involved."

The view that Landry's paralysis is initially, or at least at some stage of the disorder, a radiculoneuritis has, over the years, been strongly supported by some and denied by others. Among earlier workers in the field there were those who believed that the disorder primarily involved anterior horn cells and cranial nerve nuclei because of the paucity of sensory symptoms and the rapid development of paralysis and its even distribution and contiguity of spread (33, 50, 104, 145, 177, 184, 196, 204, 212, 214) according to this view, Landry's paralysis is a disease entity. There were others who observed virtually identical cases, except that at one stage or another sensory symptoms developed, and hence they regarded the disorder as a whole, whether accompanied by sensory disturbances or not, as primarily a form of acute polyneuritis or radiculoneuritis (63, 64, 65, 116, 118, 144, 172, 191, 215). In a review of 93 cases of "Landry's paralysis" reported in the literature up to 1889, Ross (175) concluded that the disorder was a form of peripheral neuritis inasmuch as sensibility was definitely affected in 82

Walton (220), analyzing 29 additional cases which had been published between 1889 and 1895, found that sensibility was altered in 24, and he therefore aligned himself solidly with Ross, as did Schmaus (182) in an extensive review of the subject up to 1904.

Further support of this view came in 1925, from Granger Stewart (194), who, in a meticulous comparison of Landry's paralysis (the true ascending type) and acute febrile polyneuritis and acute infective polyneuritis, stated that he had observed several cases of Landry's paralysis and over 20 cases of acute toxic polyneuritis, and that in the latter the diagnosis was based solely on the development of sensory disturbances 10 to 14 days after the onset of the paralysis, and that had death occurred before, they could certainly have been accepted as conforming to Landry's original description. Similar observations have been made by others (2, 35, 116, 211). And in his Morrison Lectures in 1932, Collier (43) stated, "I hold, as did Ross and Bury (176) in 1893 that it (Landry's paralysis) is a highly distinctive and typical form of peripheral neuritis, and that every grade of transitional form between the rapidly spreading Landry's paralysis and the slowly advancing usual types of peripheral neuritis of unknown cause may be met with." Apparently clinching the argument were the reports of Mills and Spiller (140) and Pfeiffer (158) who described ascending paralysis with minimal sensory symptoms in which degenerative changes were found in anterior and posterior roots post mortem.

Among those who more recently have opposed the clinical separation of Landry's paralysis and the Guillain-Barré syndrome were Benedek and Juba (18), Juba (111), Mirus (141), and Walshe (218), all of whom regarded the Guillain-Barré syndrome as a benign form of polyradiculoneuritis, and Landry's paralysis as a malignant form of the same disorder. Juba and Mirus referred to the malignant form as "polyradiculoneuritis ascendens."

9 Evidence of Neuraxial Involvement Numerous writers, including Boudin (24), have expressed the opinion that in the Guillain-Barré syndrome the morbid process affects solely the more proximal part of the peripheral nervous system. Others have contended that the neuraxis also is involved, though to a *limited degree*, because of 1) the frequency with which ataxia occurs when sensory deficit is neither marked nor widespread, 2) the symmetry of the progressive involvement of the limbs with the advance of the morbid process, 3) the long delay in the return of reflex activity after sensibility and motor power have been restored, and 4) the development of symptoms closely resembling those met with in tabes dorsalis, such as loss of appreciation of deep pressure, joint position, and vibration (6, 16, 82, 92, 93). (Some of this evidence could be turned in favor of sole radicular involvement—ataxia, for instance, which may occur when only the roots are affected, as Dejerine [51] first demonstrated in 1883 in a case to which he referred as "nervo-tabes périphérique.")

That the spinal cord may be affected has also become apparent from the observations of 1) occasional spasticity (10, 162), 2) the presence of the Babinski response (see under *Reflexes* in subsequent text), and 3) the occurrence of symptoms resembling those in syringomyelia (59). In a recent publication, Barré (13) presented 4 typical cases of the syndrome Guillain and he had de-

scribed, in which he adduced evidence that the pyramidal tracts were affected, he left open the question as to whether the fibers were involved in the anterior horns or in the lateral columns of the spinal cord. Gowers (89) expressed the opinion, on clinical grounds, that the main site of the attack was in terminals of the pyramidal tracts. Goebel (84), in citing a case in which tendon reflexes were exaggerated in "Landry's paralysis," stated that "Die Combination mit frühzeitigen acut myelitische Symptome mit Steigerung der Patellarreflexe bilden kein Hinderniss mehr, der jeweiligen Fall der Landry'schen Paralyse zuzurechnen," a reiteration of what Eisenlohr (65) had contended in 1874.

B Mode of Spread

The means by which a noxious agent becomes disseminated in spinal roots and proximal parts of cranial nerves, whether by way of the blood stream, lymph, or neural pathways, or by a combination of these routes, is still in the realm of hypothesis. On the basis of post-mortem studies which have disclosed marked vascular engorgement of roots, spinal cord, and leptomeninges, it has been assumed by some (15, 94, 185) that the primary or basic disturbance is vasoparalysis, and that the progression of the disorder is due to paralysis of more and more vessels. Others (43, 126) have expressed the opinion that in paralysis starting in one limited area and advancing to segment after segment, the *materie morbi* travels from the peripheral nerves into the neuraxis, through which it spreads. Another opinion is that the noxious agent spreads by way of the spinal fluid (130, 152, 219), that on reaching the roots via blood stream or lymph, the agent is diffused in the spinal fluid, affecting root after root, thereby giving rise to a clinical picture indistinguishable from that which would occur with purely neuronal spread in the neuraxis.

C The Form Characterized by Equal Disturbance of Motility and Sensibility

The form of the disorder characterized by paralysis and anesthesia, first referred to by Landry (120), has been repeatedly described (10, 34, 59, 105, 115, 130, 180, 197, 217, 219). In some of these, e.g., in Strauss and Rabiner's (197) cases, paralysis and anesthesia remained stationary at certain segmental levels, whereas in others, e.g., that of Wadsack (217), paralysis and anesthesia began in the lower limbs and ascended the trunk. In a discussion of Strauss and Rabiner's cases, referred to as instances of "myeloradiculoneuritis," Archambault remarked "To my mind, it is rather unfortunate that a new name should be coined every time a fresh group of cases arises, merely on the basis of some minor and frequently inconstant differential feature. One cannot help but feel that all these cases (those of Landry, Holmes, Kennedy, and Guillain, Barré and Strohl, etc.) catalogued under different designations have much in common, indeed the analogies are numerous and striking, and the differences negligible."

D The Varying Terminology of the Disorder

A point which needs comment is that of the autonomy of the cases which over the years have been diagnosed by terms other than Landry's paralysis and

Guillain-Barré syndrome Designations have been employed by some to emphasize the outstanding clinical characteristics, by others to highlight a supposedly infectious nature, and by still others to denote neuropathologic features

Osler (146) first and then Gordon Holmes (103) referred to the disorder as "acute febrile polyneuritis" According to the description given by Osler, the onset resembled that of an acute infectious disease, the temperature was elevated at the onset and then rose rapidly, as high as 102 or 104°F. Holmes' series comprised 12 cases which he encountered mainly in France during World War I, 2 were fatal The temperature in some cases did not exceed 100°, but in others it rose to 102° or 103°F. Spinal fluid studies were made only on 3, with completely negative results It is apparent that aside from the frequency of fever and the amount of spinal fluid protein, the cases of Holmes are in the same category as those described subsequently by Guillain Moreover, fever has been observed in cases of acute ascending paralysis, Thorner, Alpers and Yaskin (205), for instance, having found in a review of the literature that fever occurred in 25 per cent of 103 cases Collier (43), in considering this point, remarked, "I find it hard to believe that there is any type of neuritis which can be separated off *sui generis* as a clinical and etiologic entity on account of the presence of fever"

As to the adjectives "infective" and "infectious", there is considerable clinical evidence that they are justified, but until an agent is discovered the infective or infectious nature of the disorder must remain presumptive

The disorder was given the name "neuronitis" by Foster Kennedy (115) in an effort to distinguish it from the other neuritides. "I propose . . . to describe certain cases . . . revealing definite clinical variants from the syndrome of polyneuritis as we have known it, which, when considered along with the widespread changes in the posterior ganglions, spinal roots, ventral cornual changes and Betz cells of the cortex, would seem to make it fitting to remove this disease from the neuritides proper, and to designate it by a title more descriptive of the clinical and pathologic picture produced" Mills (139) is said by some writers to have coined the term, but this is not true he stated that "They (Landry's paralysis, poliomyelitis, et cetera) are perhaps what might be termed 'neuronitis,' and this term has been suggested, but seems to have an unnatural sound even to a neurological ear" Adolph Meyer (137) regarded the expression neuronitis "a little awkward", Wechsler (222) "barbarous", Collier (43) "ugly", and Kinnier Wilson (224) "superfluous"

A number of authors (123, 150, 159, 210) referred to the disorder as "polyneuritis with facial diplegia", some believing this to be an autonomous disorder, but Taylor and McDonald (200), in expressing the consensus, stated: "We cannot too strongly insist that there is no justification for singling out this symptom complex as independent, except superficially in its striking clinical manifestations"

The term "schwannitis" took hold among a few writers (11, 49, 77) who believed that the disorder was due to a neurotropic virus which specifically attacked Schwann cells, causing them to proliferate out of proportion to the

damage inflicted on the neural elements. While it is true that Schwann cells proliferate to a marked degree in this disorder, the evidence indicates that the proliferation is secondary to myelin and axonal damage. Dechaume (49), the originator of this view, based his opinion on observations in 3 fatal cases having a duration of 3, 8, and 8 weeks respectively, a time at which all changes in the peripheral nervous system are well advanced.

The term "polyneuritis" and its variations seem most frequently to have been employed for the disorder in question. There is no gainsaying that this term is justified from a clinical standpoint in many cases, and according to numerous writers, pathologically as well, even when an inflammatory exudate is absent. As Wartenberg (221) has remarked, "the term 'polyneuritis' should be used even if there is not 100 per cent inflammation and even if there is more than the involvement of the peripheral nerves—the reason being a *potiore fiat determinatio*." But the term is too nonspecific, for it does not distinguish the disorder under consideration from the great variety of neuritides in which the cause is known; moreover, it gives emphasis to only one of the many facets of the disorder. Kinnier Wilson (224) stated of this condition that "'polyneuritis' is a misnomer, or at least scarcely represents the facts, clinical and pathological." He favored "toxic degeneration of the neuron" as descriptive of the disorder, but admitted that the term was cumbersome.

E General Conclusions Based on the Literature

From the foregoing review of the literature, it may be gathered 1) that the term Landry's paralysis has, through common usage, been confined to only one of the three forms Landry described, namely a strictly motor disorder which begins in the lower limbs and advances steadily upwards, 2) that a comparable descending form, starting in realm of the cranial nerves, occurs, 3) that the Guillain-Barré syndrome, as originally described, is a disorder in which motor involvement is striking, but in which the degree of sensory involvement varies considerably but is not total, the syndrome constituting a certain narrow group within the broad confines of the malady by virtue of the restrictions placed by Guillain and Barré on the amount of protein and the number of cells in the spinal fluid, 4) that a form characterized by an equal involvement of motility and sensibility exists, and 5) that many forms, the majority in fact,⁵ bridge the gaps between the four mentioned. The literature strongly indicates that from the clinical standpoint all forms are initially polyradiculoneuritis. There are indications that the morbid process may also involve the neuraxis. It has been suggested that the noxious agent may extend from the involved roots either 1) into the spinal fluid, reaching other roots and/or the spinal cord, or 2) into the spinal cord directly by way of neuronal pathways. In any event the outcome is dependent on the degree of involvement of respiratory or cardiac nerves or their intramedullary centers.

⁵ In a series of 70 cases of "syndrome Guillain Barré Strohl," all nonfatal and all manifesting albuminocytologic dissociation, Riser and Planques (168) regarded only 18 as conforming in all respects to the cases reported by Guillain and Barré.

Because of the inadequacies of pathoanatomic terms now employed, it would seem necessary to resort to an eponymic designation. Proper names are frequently more enlightening than purely descriptive pathoanatomic terms. Laurence-Moon-Biedl syndrome and von Recklinghausen's disease, for instance, indicate far better the pleomorphic features of these disorders than do any series of pathoanatomic terms. No names are more indelibly linked to the disorder than those of Landry and Guillaum and Barré, for which reason the term "Landry-Guillain-Barré syndrome" is chosen. This term takes cognizance of the kinship of the cases described by Landry and by Guillaum and Barré and emphasizes the potentially serious nature of the disorder. The designation "Landry's paralysis" would have sufficed had Landry's descriptions been more detailed. In correspondence received by one of us, it was asked "How can you combine two diseases—one which allegedly kills and the other which should be 100 per cent benign?" Foregoing pages have emphasized 1) that Guillaum has conceded that the syndrome described by Barré and him may be fatal, and 2) that the mortality rate of 20 per cent reported by Landry is lower than that reported by others in cases designated Guillaum-Barré syndrome.

There are those who have advocated that the terms "Guillain-Barré syndrome" and "Landry's paralysis" be discarded. The Guillain-Barré syndrome, according to Margulis (131), is nothing more than a polyneuritis in which the roots are electively affected, and therefore does not merit consideration as a special form of polyneuritis. Quite the contrary it is for that very reason (i.e., because of the widespread involvement of the more proximal part of the peripheral nervous system) that the Guillain-Barré syndrome together with the other forms of the disorder should be regarded as clinically distinct, and it would seem inadvisable, therefore, as long as etiology is obscure, to attempt to discard a term which has come into such general usage. Lewey (124), of much the same mind, stated "What is, after all, left of the original Guillain-Barré syndrome since Guillaum himself has rescinded it so thoroughly and deprived it of all its former characteristics? As far as I can see, there remains only the generally accepted experience that there occur small epidemics of polyneuropathies with occasional encroachment upon the spinal cord, the brain stem and cortex, possibly of viral etiology, some of which are amazingly benign despite their threatening initial appearance, while others show a high mortality. Nevertheless, it may be more practical to accept the popular designation (Guillain-Barré syndrome) and to redefine it than to replace it by six or more long, awkward, and purely descriptive titles."

Among those who expressed the opinion that the term "Landry's paralysis" be dropped were Roseman and Aring (173) who agreed with Madelaine Brown (29) that the case Landry described in detail was one of an ordinary vitamin deficiency neuritis and therefore does not merit a separate designation. This viewpoint seems untenable, for, granting that this patient was suffering from vitamin deficiency, it is illogical to assume that the other nine referred to by him were in a similar state. If the Landry-Guillaum-Barré syndrome is an infectious disorder, a vitamin deficiency may possibly serve as a predisposing

factor Walshe (218) has remarked "Only by procrustean exertions can avitaminosis be fitted into the clinical pictures we are considering [Landry's paralysis and acute febrile polyneuritis] " Also Cobb and Coggeshall (41) proposed that the term be eliminated, but for another reason. They stated that inasmuch as the term Landry's paralysis had come to be used so loosely, now being employed mostly in fulminating cases of poliomyelitis, it is best to discard the term entirely. Considering this point, Taylor and Clark (199) stated that "if we mean by Landry's paralysis what Landry described, it is evidently absurd to arbitrarily extend the meaning of the term on the clinical side to various conditions which he did not describe " It is important to recognize that the terms "acute ascending paralysis" and "Landry's paralysis" are not interchangeable the former is observed in many disorders of known etiology, and the latter refers to an ascending paralysis of unknown etiology. The term "Landry's

TABLE 2

*Month of Onset of Fifty Fatal Cases of Landry Guillain Barré Syndrome**

JAN	FEB	MARCH	APRIL	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
5	4	7	3	5	3	3	5	3	2	5	5

* As far as could be determined all cases occurred north of the equator

TABLE 3

Age Incidence of Fifty Fatal Cases of Landry Guillain Barré Syndrome

15-19	20-25	26-30	31-35	36-40	41-45	46-50	51-55	UNKNOWN
3	19	11	10	3	1	0	1	2

paralysis" is too strongly entrenched in the literature to be abolished by edict. What should be abandoned is the misuse of the term.

III. CLINICAL OBSERVATIONS⁵

In our group the disorder displayed no particular seasonal incidence (table 2). The ages of the patients varied from 18 to 51, but the highest incidence was during the third decade of life (table 3). These data are of course influenced by the source of the cases, which was chiefly the Army, in which most of the men were between 18 and 38 years of age. Clear cut dietary deficiency associated with chronic alcoholism was noted in only 2 instances (cases 19 and 43). One patient had received Japanese B vaccine twice within 10 days of the onset of his illness (case 11), another had been vaccinated for smallpox 10 days previously and still had an intense local reaction (case 42), and 2 others had received smallpox vaccination and other immunizations 3½ weeks and "a short time" pre-

⁵ This paper is not concerned with the problem of treatment, but in view of the alleged beneficial effect of neostigmine therapy (186, 201) it should be mentioned that the drug was used in one of our cases, but to no avail (case 43).

vously (cases 46 and 23 respectively) Tetanus toxoid had been injected 12 days before the onset in another instance (case 22). Among the group there were 2 associated with infectious mononucleosis (cases 4 and 5) which have been previously reported (156, 167). One other case of this series (case 23) has also been previously published (21)

A. Prodromal Symptoms

Systemic and local infections ushered in the disorder in all save 10 cases (table 4) Upper respiratory infections headed the list, being present in 29 cases, or 58 per cent of the series The infection was generally in the acute or subacute stage when the nervous system was attacked, but in 9 instances there was a latent period of from 2 to 7 days between cessation of prodromal disorders and onset of neural symptoms In only 5 was there an elevation of temperature at the time when the neural symptoms appeared

Of the unusual prodromes the following 6 may be mentioned: In one, superficial scratches of the left leg became infected, leading to gangrenous ecthyma, and in 6 weeks, when improvement had set in, to numbness of the upper limbs and then to paralysis (case 34) In another, the buttocks became chafed by a new pair of trousers, cellulitis developed, and in 4 weeks, when healing was in progress, there was a sudden onset of diplopia and other manifestations of the disorder (case 26) In a third, severe diarrhea⁷ lasting 3 days and then subsiding, was followed on the sixth day by pain in the lumbar region and then by extreme weakness of the legs (case 28) In a fourth, watery diarrhea and facial herpes developed on the morning of the onset (case 18) In a fifth, there had been infectious hepatitis, the symptoms of which had greatly receded 3 weeks before the onset of neural symptoms (case 37) And in a sixth, multiple shell fragment wounds of the legs, buttocks, and cheek had been sustained 12 days before the neural disorder began (case 22)

B. Mode of Onset

In the majority of cases, the onset was marked by disorders in the limbs (table 4) In somewhat more than half, the initial symptoms consisted of numbness or paresthesias or pains, while in approximately one-third the first complaint was that of weakness or paralysis Often sensory and motor symptoms seemed to set in simultaneously.

Numbness and paresthesias were virtually always experienced in the distal portions of the limbs, and pains tended to occur most often in proximal portions Not infrequently the paresthesias were sharply localized at first one soldier,

⁷ Although most workers have regarded the upper respiratory tract as the initial locale of the causative organism in this disorder, there are some who have favored the gastrointestinal tract in this respect (40, 76, 143, 161) Disturbances of bladder function as a presenting symptom also have been noted (100, 117, 164) In 73 non-fatal cases of the Guillain-Barré syndrome reported by various authors in the 1938 volume of *Journal belge de neurologie et de psychiatrie*, gastrointestinal or bladder disturbances ushered in the disorder in 14 per cent

while attending a "movie," became aware of numbness of the feet, and in an hour or two, of the hands (case 16), another, while drilling, felt numbness and a tingling sensation in all his finger tips (case 37), and a third was on a hike when the great and medial toes of both feet became numb and remained so for 5 days before the disorder spread further (case 46). Pain also was sometimes well delimited, starting, for instance, in the lumbar region and radiating downward along the course of the sciatic nerves (case 28), but more frequently it occurred in several places at the same time. Pains were more commonly encountered in the legs and lower trunk than elsewhere.

The initial sites of weakness or paralysis were as follows: lower limbs, 22, upper limbs, 7, muscles supplied by cranial nerves, 7, and the bladder, 1, in the remaining 13 cases the progress was so rapid that two or more parts of the body were apparently attacked simultaneously—all the limbs in 6 instances, and limbs, trunk, and muscles supplied by cranial nerves, in varying combinations, in the remaining 7. When weakness was the first manifestation of the disorder, it often struck suddenly while the individual was engaged in activity. Thus, in one instance a soldier was driving a truck when he noticed weakness of the left leg on pushing in the clutch (case 11), in another, weakness of the arms developed while the soldier was on a rifle range, and on the return march his legs became weak (case 14), while in a third there was decreased power of the middle fingers of the right hand which lasted 3 days before the disorder progressed further (case 12). Weakness was often generalized at first, but after a variable time, usually within a few hours, paralysis could be detected either in the upper or in the lower extremities, or over the entire body. The initial general nature of the disorder in some instances is illustrated in case 9. The patient had been in the hospital 9 days with an upper respiratory infection from which he had almost recovered, when one morning he awoke unable to sit up, turn over in bed, speak clearly, or close his eyes.

As to the site of initial paralysis in the limbs, it was most frequently proximal in the lower limbs and distal in the upper (table 4). This is of interest in view of the frequent observation that proximal muscles are the site of primary attack in both lower and upper limbs (25, 35, 72, 115, 200). On this point, Thorner, Alpers and Yaskin (205) stated that "The paralytic symptoms are most often noted first in the large muscles of the thigh or the upper portion of the arm. This is not conclusive evidence that these muscles are affected first, as the larger muscles labor under greater mechanical disadvantage than the small muscles of the hands and feet. Thus some degree of weakness would be noted first in the larger muscles." Regardless of its site, the initial paralysis in our cases was invariably of the flaccid type and remained so throughout the course. Fibrillation of muscles was not observed, and it is known to be rare in this disorder, Adler and Hoff (2) being among the few who have noted it.

Ataxia of the affected limbs, out of all proportion to weakness, was observed from the onset in about one fourth of the cases. The ataxia was manifested in various ways, such as swaying on standing, staggering on walking, and exhibiting dysmetria in performing heel to knee or finger-to nose tests. Ataxia as a promi-

TABLE 4

Clinical and Laboratory Data on Fifty Fatal Cases of Landry-Guillain-Barré Syndrome

(+ signifies positive, 0, negative, and —, information not available)

CASE NO	AIR ACC NO	PRODOMAL SYMPTOMS AND REMARKS	UPPER RESPIRATORY INFECTION	CLINICAL DATA AFTER ONSET												SPINAL FLUID (N = Normal) (C = Cisternal Fluid)																
				Duration from onset to death	Temp (1) Admission, (2) Midcourse, (3) Terminal	Remarks on clinical course	Sensory symptoms				Sites of onset of paralysis (P = Proximal, D = Distal)				Cranial nerve palsies (day of onset)						Total protein mg per 100 ml	Randy reaction	Cells (per c mm)	Days tests done after onset (PM = postmortem)								
							Numbness and/or paresthesias	Pain (++) Aching (+)	Tenderness of N's and/or M's	Hyper-, hyp- or anesthesia	Reduced deep sensibility	Lower limbs	Upper limbs	Trunk (S = Sacral N's)	Cranial nerves	VIIIb	IIIb, IVb & VIIb	VIIb, Motor (M), Sens (S)	XIIIb	Dysphagia					Dysarthria and/or aphonia	Day of onset	Respiratory paralysis	Intercostal paralysis				
1	100498	Cough, sore throat, fever, 2 days One week later, apparently well when neural symptoms began "Cold" for 3 wk No cough	+	2	98.4 97.8 98	Aching, legs and shoulders, in evening Next A M legs and trunk paralyzed, upper limbs weak	-	+	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	74	-	110	2 PM (C)		
2	37602		+	3	98 98.2 98	Pain, rt leg, left face Few hr later, paralysis, legs, then arms Diplopia Sudden cyanosis and death	-	++	-	0	0	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3	82852	"Cold" 3-4 week Two days before admission, sore throat, cough, rales 9th day, afibrile, when neural symptoms began	+	3	98.2 99 96.4	Numbness and tingling all limbs, widespread paralysis, with legs least affected Could not raise head Impaired convergence O S Numbness ascended "from bottom upwards" Marked sinus arrhythmia	+	0	-	0	0	+	+	+	+	+	+	+	+	+	0	2	-	0	1	1	1	-	-	-	-	-

4	151166	Infectious mononucleosis of about 12 days' duration	+	3	97 100 4 102	Paresthesias hyposthesias and weakness all limbs especially lower depressed gag reflex 2d day severe paralysis incl dia phragm 3d stiff neck pos Kernig convulsion and sudden death	+	-	-	+	+	+	0	+	+	+	+	1	-	-	2	-	3	-	-	81	-	60 30	3
5	163849	Infectious mononucleosis of about 18 days duration	+	4	97 98 98 6	Weakness all limbs calves and thighs tender Next day paresthesias feet and hands 2d lower limbs and trunk useless upper limbs weak 3d speech nasal	+	-	+	+	-	-	-	0	0	+	-	-	0	-	3	3	3	3	74	-	8	1	
6	81835	Coryza with cough 2 days	+	4	100 3 97 4 98 4	Awoke with generalized aches and pains and severe weakness 3d day legs paralyzed arms normal 4th paralysis all limbs and access resp m a Severe hiccups Persistent pri apnea	++	-	-	-	-	-	-	0	0	+	-	-	-	4	-	4	4	N	-	1	3		
7	44275	Head cold in evening Next A M neuralsymptoms began	+	4	98 4 98 100 6	Weakness and numbness, legs Next day paralysis legs weakness arms 3d analgesia and paralysis which ascended to Th V Sudden death	+	-	-	-	-	-	-	+	+	+	-	-	-	2	-	4	4	-	+	-	1		
8	102159	One week before onset admitted to hosp with painful swollen testis Frequent pharyngitis	+	4	98 6 99 8 102	Weakness, arms legs trunk then paralysis	0	0	0	0	+	+	+	0	0	0	+	-	0	0	0	0	2	2	-	-	3	1	
9	93717	Cold 3-4 wk Two days before admission cough sore throat rales 9th day almost well when neural symptoms began	+	4	98 98 102 4	Acute generalized weakness Could not sit up, turn over speak clearly or close eyes 3d day patchy hyposthesias and hyperalgesia distal parts of limbs sinus arrhythmia pulmonary edema	-	-	-	+	+	+	-	+	+	+	+	1	-	3	3	1	2	2	100	+	2	3	

CASE NO	AIR ACC NO	PROXIMAL SYMPTOMS AND REMARKS	CLINICAL DATA AFTER ONSET															SPINAL FLUID (N = Normal) (C = Cerebral Fluid)										
			UPPER RESPIRATORY INFECTION	Duration from onset to death	Temp (1) Admission, (2) Midcourse, (3) Terminal	Remarks on clinical course	Sensory symptoms					Sites of onset of paralysis (P = Proximal, D = Distal)				Cranial nerve palsies (day of onset)						Respiratory paralysis	Day of onset	Intercostal paralysis	Total protein mg per 100 ml	Randy reactions	Cells (per c mm)	Days tests done after onset (PM = postmortem)
							Numbness and/or paresthesias	Pain (++) Aching (+)	Tenderness of N's and/or M's	Hyper-, hyp- or anesthesia	Reduced deep sensibility	Lower limbs	Upper limbs	Trunk (S = Sacral N's)	Cranial nerves	VIII	III, IVb & VIb	Vb, Motor (M), Sens (S)	XIII	Dysphagia	Dysarthria and/or aphonia							
18	11783	Atabrine for malaria 5 days before onset Watery stool A M of onset Herpes on face	-	6	101 99 98	Numbness, hands & legs, unsteady gait, headache, facial herpes Then weakness, hands and arms Next day, patus in calves Somnolent 3d, dysphagia	+	++	+	H H	+	+	D	+	+	+	+	+	+	+	4	1	+	42	1	7	1	
19	92275	Alcoholism and poor diet Two wk before onset, sore throat, malaise, aching muscles	+	6	101 99 98	Weakness, rt upper limb, then left Next A M lower limbs weak Blurred discs Progressive paralysis and ascending loss of sensation to L II Hyperalgesia at Th II Paralysis, trunk, left vocal cord, palate, access resp m's Neck stiff, pos Kernig Cardio death	-	+	+	H H	+	D	+	+	+	0	0	0	0	4	4	-	76	+	25	4		
20	155614	For 5 mo tremor, apprehension Mild resp infection shortly before onset	+	6	99 99 98	Numbness, fingers and toes, which ascended Then ataxia, limbs and pain in arms, back and legs 3d day, paralysis, all limbs	+	++	+	-	+	+	D	+	+	+	0	0	0	0	4	3	+	34	+	5	4	

TABLE 4—Continued

CASE NO	APR ICC NO	PRODROMAL SYMPTOMS AND REMARKS	UPPER RESPIRATORY INFECTION	Duration from onset to death	Temp (1) Admission, (2) Midcourse, (3) Terminal	Remarks on clinical course	CLINICAL DATA AFTER ONSET										SPINAL FLUID (N = Normal) (C = Cisternal Fluid)											
							Sensory symptoms					Sites of onset of Paralysis (P = Proximal, D = Distal)				Cranial nerve palsies (day of onset)					Day of onset	Respiratory paralysis	Intercostal paralysis	Total protein mg per 100 ml	Randy reaction	Cells (per c mm)	Days tests done after onset (PM = postmortem)	
							Numbness and/or paresthesias	Pain (++) Aching (+)	Tenderness of N's and/or M's	Hyper-, hyp- or anesthesia	Reduced deep sensibility	Lower limbs	Upper limbs	Trunk (S = Sacral N's)	Cranial nerves	VIII	III, IVth & VIth	Vth, Motor (M), Sens (S)	XIIth	Disphagia								Dysarthria and/or aphonia
27	03298	"Head cold" 1 wk, then admitted to hospital where improvement had set in	+	9	99	Numbness rt face and rt side of mouth and teeth (2d and 3d divisions of Vth N) Next day, severe pain and paralysis, arms and rt leg Cardiac death	+	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	9	7	
28	118904	Severe diarrhea 3 days, improvement on 4th, when neural symptoms began	-	10	98 2	Sharp pain, lumbar region, radiating down back of legs 3d day, paralysis, legs and trunk, fingers, weak 4th, paralysis, abdominal wall	-	++	0	-	+	P	D	+	+	+	+	+	+	+	+	+	+	+	+	+	5	3
29	179944	Sore throat and slight cough for 4 days	+	10	98 2	Numbness, hands and feet, pain, lower trunk, then weakness, legs and arms 5th day, progressive paraplegia with "ascending" paralysis and with ascending loss of sensibility and bladder incontinence	+	++	-	0	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	8

30	179945	Cold' with cough for 0 days On admission rates in chest Heavy drinker	+	10	09 101 104 2	Numbness, rt foot and leg and dull back pain 2 days later numbness left foot and difficulty in walking 6th anesthe- sia up to Th XII flaccid paraplegia 7th paraly- sis and anesthesia up to Th V 9th severe pain arms	+++	-	+	+	+	+	-	-	-	-	8	-	-	-	18	0	2	3			
31	92536	-	-	10	97 2 101 107	Difficulty in moving legs while drilling Col lapsed Next day pa- ralysis legs then arms 3d loss of gag reflex ach- ing legs 7th sinus tachycardia	0	+	0	0	+	+	+	-	-	-	-	-	3	3	4	-	30	-	0	7	
32	100230	In hospital 10 days with febrile up- per resp infec- tion when neural symptoms began	+	10	93 98 2 108 8	Weakness and tremors arms and legs Next day paralysis all limbs pain in elbows	0	+++	-	-	+	+	D	-	-	-	-	-	0	-	0	6	-	0	5	6	
33	141170	For 3 wk night sweats chilly sensation no sore throat Colds all win- ter	+	11	-	Tingling fingertips Next day, splitting headache severe pain in calves staggering then paraly- sis of lower limbs 3d arms weak 7th disorien- tation insomnia paraly- sis of access resp in s	+++	+	+	+	+	+	-	-	-	-	7	0	3	0	7	7	100	+	2	6	
34	127601	Scratches left calf then gangrenous ecthyma both legs Almost well 6 wk later when neural symptoms began	-	11	-	Numbness hands ascend- ing to mid arms gener- alized severe weakness and ataxia all limbs 6th transient blurring of vision 8th paralysis palate and pharynx	+	-	-	+	+	+	-	-	-	-	-	-	9	8	8	8	110	+	30	10	
35	43912	-	-	12	99 2 97 8 99 4	Weakness legs Calves ached back pained On 4th trunk and arms very weak 6th almost total helplessness unable to move or change position of head Insomnia	+++	-	-	-	+	+	P	-	0	0	-	-	-	6	-	12	-	-	0	4	0

TABLE 4—Continued

CASE NO	AIR ACC NO	PRODOMAL SYMPTOMS AND REMARKS	UPPER RESPIRATORY INFECTION	Duration from onset to death	Temp (1) Admission, (2) Midcourse, (3) Terminal	Remarks on clinical course	Sensory symptoms						Sites of onset of paralysis (P = Proximal, D = Distal)				Cranial nerve palsies (day of onset)						Total protein mg per 100 ml	Pandy reaction	Cells (per cmm)	Days tests done after onset (PM = postmortem)		
							Numbness and/or paresthesias	Pain (+) Aching (+)	Tenderness of N's and/or M's	Hyper-, hyp- or anesthesia	Reduced deep sensibility	Lower limbs	Upper limbs	Trunk (S = Sacral N's)	Cranial nerves	VIII	VII, IVth & VIth	Vth, Motor (M), Sens (S)	XIIIth	Dysphagia	Dysarthria and/or aphonia	Day of onset					Respiratory paralysis	Intercostal paralysis
36	172602	—	—	12	98 4 98 8	Weakness and paresthesias, legs, then arms 3d, partial paralysis By 4th, unable to move limbs or trunk, blurring of optic disc 5th, analgesia, limbs	+	+	+	A	+	+	+	+	+	+	+	+	+	+	5	+	+	10	85	+	10	6
37	94760	Infect hepatitis starting 7 wk prior to onset and lasting 1 wk	—	13	98 2 98 8	During drill, numbness and tingling, finger tips, both hands Next day, hands and toes numb By 5th paralysis, arms and legs, and generalized muscle pain Sudden resp death	+	++	+	A	+	D	+	+	+	+	+	+	+	+	9	+	+	13	—	0	—	7
38	145829	Chest cold and cough for 2 wk History of acute CNS disorder 13 yr previously	+	13	98 6 98 6 102	On arising in A M, very weak and pains in limbs and lower trunk 3d day, quadriplegia, 6th, paralysis, left diaphragm Neck stiff, pos Kernig	—	++	+	—	+	D	+	+	+	+	+	+	+	+	—	+	+	4	50.5	0	8	4
39	34713	—	—	14	97 6 98 2 98 8	Paresthesias and pains, all limbs, progressive paralysis, all limbs Died suddenly	+	++	+	H	+	+	+	+	+	+	+	+	+	+	9	+	+	—	—	+	0	9

48	85371	Headache cough chills T 104 F 2 wk later almost well when neural symptoms began	+	33	98 6	Weakness and numbness left arm Next day same in rt arm then left leg then rt numbness of mouth and impaired taste 8th diplopia 11th patchy hyperaemia limbs and astereognosis 32d headache pain in neck, complete paralysis and analgesia below neck Difficult breathing and sharp shooting pains across chest and into upper limbs 7th day, weakness lower limbs 12th paralysis visual ac- commodation 17th di- plopia 29th nasal speech and paralysis soft palate 31st weakness, all muscles including accessory resp m's hypoaesthesia L I-III, bilat	++	+	+	+	+	+	P	+	-	7	8	2	8	-	7	-	32	-	333 317	+	+	4 55	11 31
49	134232	Acute tonsillitis subsiding in 12 days Two days later neural symp- toms began	+	45	-	-	+++	-	+	+	h	+	-	-	+	11	17	1	8	-	1	41	45	-	0	1	31	35	
50	95140	Headache, nausea vomiting sore throat chills T 99°F 3 days Temp normal 1 day before neural symptoms began	+	46	98 2 98 6 97 8	Pain RLQ and rt flank vomiting Next day diarrhea diplopia nys- tagmus disorientation 12th weakness upper limbs 15th lower uri- nary and fecal inconti- nence 37th analgesia up to Th X and in entire upper limbs	+++	+	+	+	A	+	-	-	+	12	2	-	37	35	16	45	-	48 64 59	0 0 +	0 0 0	8 18 28		

nent early symptom has been noted by numerous authors, and occasionally it has been the most striking symptom (51, 192)

It is of interest in cases in which local infections ushered in the disorder, that the first neural involvement was generally at a distance from the site of infection. Thus, in 2 cases of granulating ulcer of the buttocks and legs, respectively, the first site of neural involvement was in the extraocular muscles in one and in the hands in the other (cases 26 and 34), and in another with "synovitis" of the left knee, the disorder was first manifested by weakness in the fingers of the right hand (case 12). By way of contrast there was 1 instance of ulceration of both hands in which numbness began in the hands (case 44).

In 4 of the group the disorder commenced exclusively in the domain of the cranial nerves. In one, diplopia was the leading symptom, the patient was writing a letter when he began to see double, and soon his speech became slurred, and his hands paresthetic (case 26). In another, diplopia and dysphagia were first complained of, and then ophthalmoplegia and facial paralysis set in (case 22). In still another the patient awoke unable to swallow (case 15), and in yet another the presenting symptom consisted of numbness of the right side of the face and mouth (case 27). In an additional 4 cases cranial and spinal nerves were apparently simultaneously affected (cases 2, 3, 4 and 9).

Still another category of onset was evident, namely, that characterized by abdominal pain: in one the symptoms simulated those of acute salpingitis (case 47), in another there was severe pain in the right lower quadrant of the abdomen and in the right flank (case 50), while in the third severe abdominal pain lasting 2 days was followed on the third day by urinary retention, and on the sixth by grave mental symptoms, but it was not until the eighteenth day that paralysis of the limbs set in (case 45).

C Course

The course of the disorder in this series was diverse. In cases in which the duration of the illness was short, the paralysis often spread so rapidly that the sequence of muscle involvement was not apparent. In cases of longer duration the progress of the paralysis could be more easily followed. Generally when it started in the lower limbs, it affected next the upper limbs, then cranial nerves or trunk or intercostals, suggesting that the length of the lower motor neurons was the determining factor in the progression of the paralysis. In 7 instances the paralysis began in the upper limbs, and here also the other members usually became affected before the trunk or intercostal muscles or the muscles supplied by cranial nerves. Occasionally paralysis affected limbs alternately. Thus, in case 48 the first site of paralysis was the left arm, then on the next day the right arm, followed shortly by paralysis of the left leg, then the right. In one individual the left leg became paralytic, then the left hand, the left forearm, the left cheek, and the left side of the tongue, in this order, subsequently the paralysis became bilateral (case 11). Atrophy occurred in only 2 instances in the dorsum of the hands by the tenth day after the onset in 1 (case 44), and in all the limbs by the thirty-seventh day after the onset in the other (case 50).

Atrophy in this disorder has been frequently observed (3, 36, 37, 58, 69, 81, 99, 117, 208), usually it was peripheral in location, but occasionally (168) it was proximal. Edema and swelling of affected muscles or overlying subcutaneous tissue during the acute phase of the disorder were not observed in our cases, but have been noted by others (20, 65, 66, 190, 215).

As is evident from the foregoing data, the spread of the paralysis was generally throughout much of the domain of the peripheral nervous system. How much of the paralysis was due to neuraxial involvement was impossible to decide. Thus in case 40 the disorder was ushered in by tingling of the feet, which spread upward to the knees, 3 days later the legs became weak, and after another 3 days the arms and face became similarly affected, on the seventh day dysphagia and dysarthria developed, and on the twelfth, intercostal and respiratory paralysis which led to death. The paralysis can be said to have ascended to the cranial nerves and then to have descended to involve the intercostal nerves, but whether, in addition, the spread was neuraxial, cannot be categorically stated or denied. In another instance, case 7, of 4 days' duration. Weakness and numbness started in the legs, on the next day the upper limbs became paralyzed and dysphagia occurred, and on the third day paralysis and analgesia ascended to the level of Th X. In this case there appears to have been an initial generalization of the disorder in spinal roots and peripheral nerves and it could be presumed that there was a subsequent spread by way of the neuraxis. The most suggestive evidence that the morbid process ascended the spinal cord by tissue contiguity was in case 30, and yet the symptoms may be explicable also on the basis of primary radicular involvement. Numbness developed in the right foot and leg, and dull pain in the back. Two days later the left foot became numb. Paraplegia gradually developed and became total on the fourth day of the illness, also the bladder became paralytic, and anesthesia up to Th XII was noted. Then on the fifth day paralysis spread rapidly up the trunk, involving the abdominal muscles en route, and reached the nipple line, respiratory difficulty set in, necessitating removal of the patient to a respirator. By the seventh day the anesthesia had risen to the nipple line, on the eighth, dysphagia and facial diplegia developed, and on the ninth, severe pain was complained of in both arms. Death occurred on the tenth day of illness.

Only in 3 cases can it be said with a reasonable degree of certainty that death occurred before the disorder reached the cranial nerves, in two, of 4 and 10 days' duration respectively, the paralysis became widespread in the limbs and trunk and then included the intercostals (cases 8 and 28), while in the other, of 29 days' duration, the legs and arms became paralyzed, hallucinations developed, and intercostal paralysis set in (case 47).

The course of the illness in the 4 cases in which the onset was exclusively in the domain of the cranial nerves, varied considerably. The duration was from 5 to 9 days. In 2 of these there was subsequent involvement of other cranial nerves and the limbs (cases 26 and 27), indicating widespread dissemination of the noxious agent to spinal nerves. By way of contrast, the other two (cases 15 and 22) appear to be instances of true descending paralysis. In case 22 the patient

initially experienced double vision, difficulty in swallowing, and headache. The next day ptosis developed, and the pupils were observed to react feebly to light. On the third day the speech took on a nasal quality, and ophthalmoplegia became total and the face paralyzed. On the sixth, the day of death, the right masticatory muscles lost their power, and respiratory paralysis set in. Throughout the course the legs remained unaffected, and the arms also, except during the last day when the tendon reflexes could be obtained only by reinforcement.

It will be noticed in table 4 that the duration of the respective illnesses varied from 2 to 46 days. In the cases of relatively short duration the course was steadily downhill. The same was true of the cases of longer standing, with one notable exception, namely case 48, in which there was prolonged remission followed by relapse. The patient had had a stormy illness during the first 12 days and was transferred to another hospital where a respirator was available. During the succeeding 2 weeks his general condition improved, he recovered his sense of taste, facial paralysis regressed, and he could more readily flex his right arm. Then on the thirty-second day he complained of frontal headaches, nasal congestion, and pain in the neck muscles, the paralysis of the limbs and trunk rapidly became worse, and, simultaneously, analgesia spread upward to the lower cervical region. Respiratory difficulty then developed; he could only whisper, he could not cough, and his throat had to be aspirated almost constantly because of rapidly collecting mucopurulent material. Death occurred approximately 2 days after the onset of the relapse.

Respiratory failure was the final event in the great majority of the cases. It was manifested in various ways: breathlessness, cyanosis, weakness of the voice, failure of the cough reflex and was aggravated by an inability to expel mucus from the tracheobronchial tree. The respiratory failure generally could be traced to paralysis of the intercostals, and in 4 instances there was weakness or paralysis of accessory respiratory muscles as well (cases 6, 11, 19 and 49). Diaphragmatic paralysis occurred in 4 instances (cases 4, 11, 23 and 38), and severe hiccups in 1 (case 6). Respirators usually had to be resorted to, but occasionally respiratory failure appeared with such abruptness that death ensued before a respirator could be employed. Case 37 was such an instance. Occasionally, respiratory embarrassment could be traced in part to paralysis of the vocal cords. Thus, in case 50, in which the period of survival was 46 days, slurred speech and hoarseness developed on the sixteenth day of the illness, and on the twenty-fifth day difficulty in breathing, these continued for a few days and on the thirty-first day, when the patient was aphonic, the vocal cords were found to be paralyzed. Subsequently paralysis and analgesia of the lower half of the body (to Th X) developed and then signs of pneumonia, but respiration did not fail until the day before death. Paralysis of the vocal cords was noted also in cases 13 and 19.

There were, however, several cases in which respiratory failure could not be assigned as the cause of death. In 3 of these, circulatory failure, heralded either by sudden or gradually increasing tachycardia, was the terminal event (cases 13, 19 and 27). In some an important contributory cause of death seemed to be bronchopneumonia or pulmonary edema.

D Sensibility

Pain was a symptom in 28 instances and usually ushered in the disorder. This is an incidence of 56 per cent, which is somewhat higher than in the series of 20 cases reported by Gilpin, Moersch and Kernohan (82) in which it was 40 per cent. In our series the pain was generalized in about one-third of the cases. It sometimes radiated from the lower trunk into the back of the legs, where it followed the course of the sciatic nerves (e.g., cases 16 and 28), occasionally it was of peripheral nerve distribution, corresponding for instance, to the territory of the femoral nerve (case 11), occasionally it was localized only in joints (cases 32 and 43), large muscle groups (cases 17, 18 and 33), lower trunk (cases 29, 30 and 35), abdomen (cases 12, 45, 47 and 50), or face (case 2). In one, the disorder started with sharp shooting pains across the chest and upper limbs (case 49). In only 3 of the 28 cases was the development of pain delayed until the course was well advanced: on the fifth day of a 13-day course, when generalized pains occurred (case 37), on the sixth day of a 14-day course, when contact of the heels on the bed was painful (case 40), and on the fourteenth day of a 20-day course, when pain developed in the hips and knees (case 43). As a rule the pain subsided as the disorder progressed, but occasionally it persisted or became worse. The remark of Gordon Holmes (103), "I have not seen any man with acute febrile polyneuritis who suffered with pains comparable to those of a moderate case of alcoholic neuritis," is applicable also to our series, with the exception of 4 in which the pains were described as severe or excruciating (cases 23, 27, 33 and 45). Intolerable pains, sometimes ushering in the disorder and at other times occurring late in the course, have been noted also by others (42, 83, 87, 114, 117, 168, 171, 186, 200, 207, 223).

Aching of the calves, shoulders, and elsewhere was a prominent symptom in 5 in which pains were not experienced (cases 1, 10, 24, 31 and 44).

Tenderness of muscles or nerve trunks or both were noted in 16 instances, in 3 of which no pains or aching were experienced (cases 5, 15 and 19). *Vice versa*, there were 21 instances in which aching or pain was complained of in which pressure-pain was either not present or not recorded.

Numbness and paresthesias occurred as frequently as pain, being noted in 29 cases. In about one-half of these, numbness or tingling was the presenting symptom, most pronounced at first in a distal location, occasionally spreading up the limbs (as in cases 20, 34, 40 and 41), and in 1 instance progressing for an undetermined distance "from bottom upwards" (case 3). A sensation of numbness in the region of distribution of the maxillary and mandibular divisions of the trigeminal nerve was an initial symptom in 1 instance (case 27).

Hyperesthesia or hyperalgesia or both was detected in 8 cases. A significant example is case 43 in which hyperalgesia was sharply limited to the region of distribution of L I to S V and C VI to Th I, except for analgesia at the periphery of the extremities. Hypesthesia and anesthesia were more frequent, being noted in 19. Ordinarily they remained confined to the periphery of the limbs and were of glove-sock distribution, but occasionally hypesthesia was widespread and patchy, not being confined to peripheral nerve or segmental areas, such an instance was case 46 in which hypesthesia and hypalgesia were noted in several

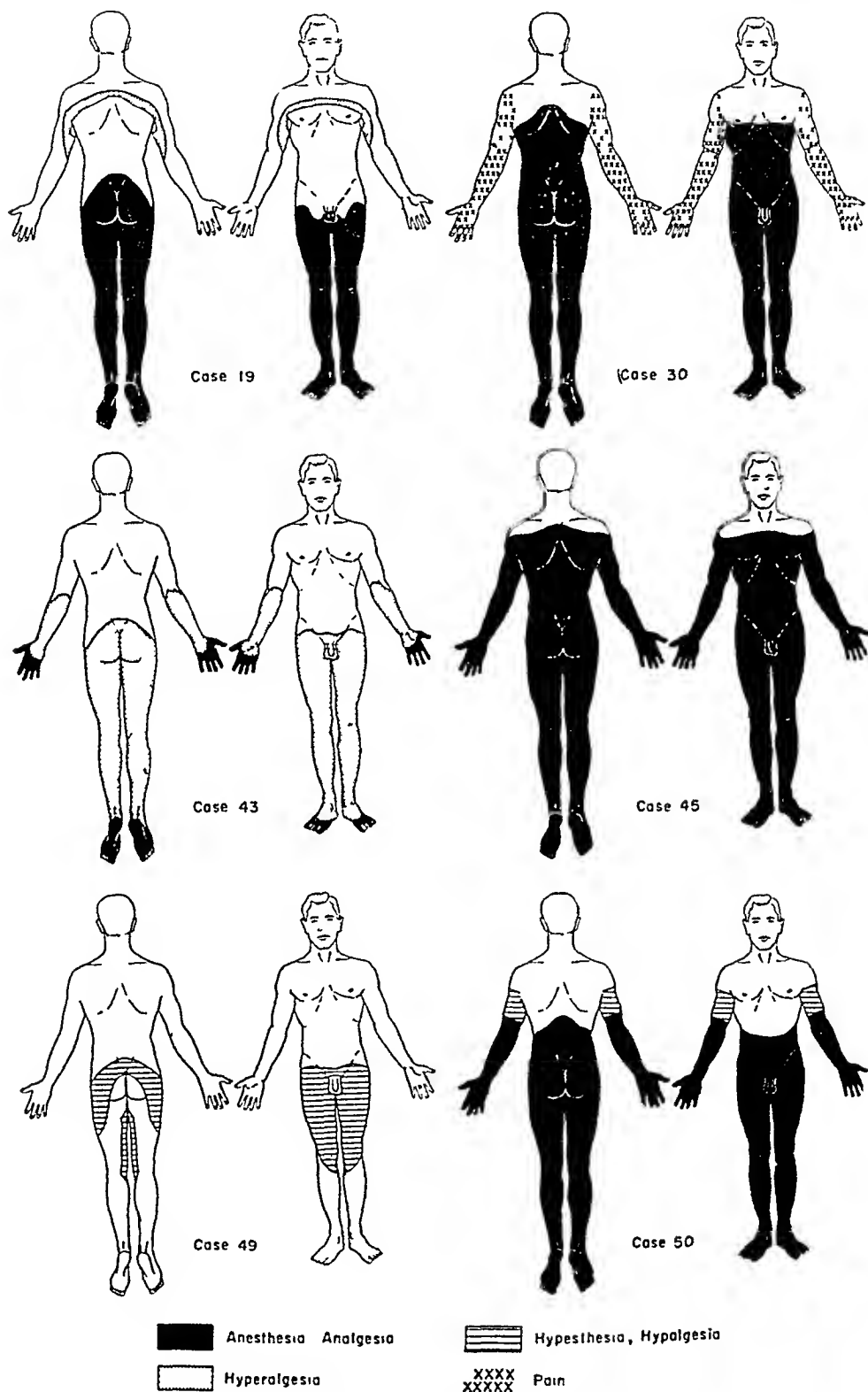


FIG 2 THE SENSORY CHANGES IN 6 CASES OF THE SERIES (AIP NEG 102342)

regions of the limbs, and in which there was a doubtful sensory level of Th XI. Such disturbances are virtually always bilaterally equal, but occasionally, as in

the case of Briskier (27), they affected only one-half the body. Reduction of sensibility of segmental distribution remained stationary in some of our cases, e.g., in segments L I to L III in case 49. In others it spread. Thus, in case 7 anesthesia ascended in 3 days to the level of Th X, where it halted. In case 19 it reached L II, while hyperalgesia was experienced at the level of Th II. Also in case 30 anesthesia spread upward, reaching the level of Th XII by the fifth day and Th V by the seventh day, on the ninth day the patient experienced severe pain in both arms, and died on the tenth day. A similar distribution of analgesia was noted in case 50, in which sensibility was lost up to the level of Th X, and over most of the upper limbs. In cases 45 and 48 analgesia over the entire body up to the lower cervical region was encountered toward the end of the respective courses. Six examples are illustrated in figure 2. Whether these are cases solely of radicular involvement or of secondary extension of the morbid process into the spinal cord can, again, not be stated categorically, but it is hard to conceive of such widespread and uniform loss of sensibility without implication of the spinal cord.

Deep sensibility suffered in 19 cases, as manifested by impaired appreciation of position, movement, and vibration—sometimes singly but generally in combination. In all, the disturbance was confined to the hands and feet, mostly the latter, and usually was apparent 2 or 3 or more days after onset of the illness. Astereognosis was noted in cases 26 and 48, this finding, relatively uncommon in the absence of other sensory changes, was a striking feature in a case described by von Sántha (213).

Of the entire 50 cases, there were only 4 in which both subjective and objective disturbances of sensibility were absent or were not recorded, all were of brief duration, lasting 4, 5, 6 and 8 days respectively (cases 8, 14, 22 and 25). Cranial nerves were affected in all except 3 (cases 8, 28 and 47).

E Reflexes

As paralysis swept through a limb, the tendon reflexes were reduced and then abolished. Occasionally they were exaggerated initially (cases 13 and 24). Where paralysis spared some muscle groups the corresponding tendon reflexes were sometimes retained. Superficial reflexes were almost always lost eventually. The Babinski reflex was elicited in only 1 instance and then bilaterally (case 15), in this patient all other deep and superficial reflexes were unobtainable. In 2 other cases the Babinski reflex was equivocal (cases 28 and 42). This reflex has been obtained by others* (10, 36, 44, 56, 132, 162, 164, 180, 183, 217). Patellar clonus in the early part of the course was noted in 1 instance (case 24). In 1 patient in whom all reflex activity was abolished, there was persistent priapism (case 6).

F Sphincter Involvement

Urinary incontinence or retention was observed in about one-fourth of the cases during earlier phases when consciousness was still preserved. Usually it

* In one instance in which a Babinski response was obtained and in which laminectomy was done, there was marked swelling of the spinal cord, which doubtless was responsible for the Babinski response (197).

was transient In 1 case urinary retention and severe abdominal pain were the presenting symptoms, but vesical function was soon restored (case 45) This incidence of sphincter involvement is higher than that usually encountered among nonfatal cases

G. Meningeal Involvement

Stiffness of the neck was encountered in 6 instances (cases 10, 15, 19, 36, 38 and 40), excluding 1 associated with infectious mononucleosis. In 5 of these a positive Kernig reflex was elicited. The spinal fluid cell count was normal in 1 of the 6, and varied between 7 and 23 per c.mm in the remainder Others who have noted evidence of meningeal irritation with the pleocytosis are listed in table 1 It is of interest that in the 2 cases with the highest spinal fluid cell count, i e , 30 and 55 cells per c.mm , no evidence of meningeal irritation was noted (cases 34 and 48 respectively) Vice versa, there are many cases recorded in the literature in which signs of meningeal irritation prevailed but in which the spinal fluid cell count was normal Of special interest is a series of 6 cases reported by Riser and Planques (168) in which a positive Kernig's sign constituted the first manifestation of the disorder (see also Riser, Planques and Géraud [169]) In 73 instances of nonfatal Landry-Guillain-Barré syndrome reported by various authors in the 1938 volume of the *Journal belge de neurologie et de psychiatrie*, symptoms of meningeal involvement were encountered in 21

H Headache

Headache was complained of in only 4 instances, and then was transient (cases 18, 23, 33 and 48) It occurred at the outset in 3 and in the latter part of the course in the fourth Subsequent severe mental changes developed in 2 of these (cases 23 and 33) Headache as a prominent symptom has been reported by others (40, 48, 117, 121, 142, 163, 168, 198, 200)

I Temperature, Pulse, Respiration and Blood Pressure

During the early course of the respective illnesses, the temperature generally was within normal limits, or was even subnormal Of the 44 cases in which the initial temperature is known, there were 5, however, in which it was slightly to moderately elevated, and of the 4 of these in which the subsequent temperatures are known, there was an early return to normal in 2 (cases 6 and 35), and a subsequent rise in 2 (cases 27 and 30) A terminal rise in temperature occurred in 23 A definitely febrile course was noted in only 3 instances In one of 5 days' duration, the initial temperature was 97.8°F, on the second day it rose to 101.8° and slowly climbed until the end, when 103.8° was reached (case 14) In the second, of 10 days' duration, the temperature on the third day of illness (the day of entrance into hospital) was 99°, on the fourth day it started to "spike" between 99 and 100.4°, on the eighth day went to 105°, in the vicinity of which it remained (case 30). And in the third, also of 10 days' duration, the initial temperature was 99°, and on the third day climbed to 102°, where it remained for 2 days, then fell to normal (case 27) At autopsy, bronchopneumonia

was absent in cases 30 and 27, but was present in case 14. The conclusion reached from a review of the clinical histories is that the fever was a manifestation of the disorder and not the result of complicating bronchopneumonia.

Pulse and respiratory rates, on the other hand, tended to be considerably elevated throughout much of the course of the illness, usually reaching a maximum at the end. The blood pressure generally remained within normal limits, but in 11 instances became elevated. An example is case 50 in which the duration of the illness was 46 days, on the fifth day the blood pressure was 122/74, the tenth, 180/100, the fourteenth, 160/114, and in the latter part of the course, 198/162. It is apparent that tachycardia and hypertension contributed to the fatal outcome in numerous cases.

J Mental Symptoms

Mental clarity prevailed in all except 7 of the cases. In one of these, the patient, during the last 5 days of a 23-day illness, had delusions, for example, that his body was divided into four parts and that some belonged to another person (case 46). Another patient became confused and heard voices calling his name on the second day of his illness, on the fourth day he announced that he had swam the English Channel, and on the sixth that he was riding a train, and on the seventh that he was on a boat, but after the ninth day his mental symptoms cleared (case 50). Hallucinations occurred in the latter part of the illness in cases 23 and 47. Transient periods of excitement, anxiety, and panic were experienced early in the course of the illness in 2 (cases 16 and 45) and late in another (case 33).

K Cranial Nerve Palsies

Aside from palsies of cranial nerves IX and X, which occurred in all save 3 (cases 8, 28 and 47), facial palsy was the most frequent (table 4). It occurred in 25 of the cases (50 per cent), was virtually always bilateral, and usually developed relatively early in the course of the disorder. In different series recorded in the literature, the incidence of facial paralysis varied considerably in 17 of 20 cases (25), in 10 of 32 cases (168), and in 6 of 20 cases (82).

Extraocular palsies were observed in 12 instances. There was ptosis in 3, palsy of a lateral rectus muscle in 4, palsy of a medial rectus in 1, weakness of accommodation-convergence in 1, total ophthalmoplegia in 1, and palsy of undetermined type in the remaining 2. Judging from the paucity of reports of paralysis of accommodation-convergence (45, 89, 145, 173, 203), it is a relatively uncommon finding, as is also total ophthalmoplegia (10, 43, 57, 77). Nystagmus on lateral deviation of the eyes was observed in 3 (cases 26, 42 and 50), and on upward gaze as well in 1 (case 42). A few others have also observed nystagmus in this disorder (78, 106, 130, 160, 162, 200, 206), in the 15 cases reported by Van Bogaert et al. (207), nystagmus occurred in 3.

The trigeminal nerve was affected in 14 instances. In 4 the disturbance was in the motor realm, in the other 10 the sensory part of the nerve was attacked, there being numbness and tingling of the lips, tongue, teeth, or face in 9, and

facial neuralgia in the remaining 1. The corneal reflexes were apparently normal in all save 3 (cases 11, 23 and 46). In 1 instance in which the mouth was numb, taste was impaired (case 48).⁹ Judging from the paucity of reports in the literature (74, 173, 198, 217, 219), impairment of taste is a rare manifestation of the disorder.

The hypoglossal nerve was implicated in 10 cases.

L Visual Disturbances

Transient indistinctness of vision was noted in 2 of the series (cases 34 and 49), and blurring of the optic disc in 2 (cases 19 and 36). In no case was frank papilledema observed, which is in contrast to the findings reported by others (40, 53, 122, 141, 164, 200, 208). Gilpin, Moersch and Kernohan (82) reported papilledema in 3 of 35 instances, in 2 of which a choking of 2 to 3 diopters was present. Retinal hemorrhages in association with papilledema has been reported (40, 164), as has optic neuritis (62, 183). Craniotomy has been resorted to in 2 cases of papilledema in which vision was threatened (71, 135).

M Herpes

Herpes of the lips was noted in 1 instance (case 9), and of the lips and face in another (case 18).

IV. LABORATORY DATA

A Virus and Bacterial Studies

Virus studies carried out by the Department of Virus and Rickettsial Diseases at the Army Medical Department Research and Graduate School on material from the nervous system in 17 cases proved negative. Cultures of spinal fluid in 8 instances and of blood in 7 also failed to reveal any organisms. On the other hand, cultures of material from the throat, lungs, and elsewhere in 13 cases disclosed a variety of organisms, with streptococci and staphylococci predominating (table 5).

B Spinal Fluid

In the 33 cases in which the total protein of the spinal fluid was determined, it varied from 18 to 372 mg per cent. If 45 mg per cent is assumed to be the upper limit of normal, the protein was in excess in 21. Where more than one determination was made, the values fluctuated; thus, in 6 instances the initial values were higher than those obtained subsequently, while in 4 others the reverse was obtained. The most striking elevation was in case 24, the total protein on the second day being 20 mg per cent, and at autopsy, done on the eighth day, 250 mg per cent. The greatest reduction was in case 28, the total protein on the third day being 114 mg per cent, and on the sixth day, 55 mg per cent. Similar observations on increase or decrease of protein as the disorder progressed have

⁹ In one case of the disorder which reached the Army Institute of Pathology after this study was completed (AIP Acc 174656), the patient complained that everything he ate tasted bitter, he also had a feeling of numbness of the tongue.

been reported by others Johnson (107), in 19 cases of "infectious polyneuritis" occurring in the Italian Theater of Operations during World War II, found in

TABLE 5

Data on Bacterial Cultures in Thirteen Fatal Cases of Landry Guillain Barré Syndrome

CASE NO	SOURCE OF CULTURE	DAY AFTER ONSET CULTURE MADE (PM = POST MORTEM)	RESULTS
4	Throat	2	A few alpha strep, nonhemolyt staph
5	Throat	3	Pneumococci, hemolyt strep
14	Lungs	PM	Staph aureus, occasional strep, rare pneumococcus, Micrococcus catarrhalis
15	Intestines	PM	E coli, B subtilis, Paracolon group (coli type) with small amount of Salmonella "O" antigenic factor III in 2 cultures and factor $\alpha\alpha$ in a third culture
22	Throat	3	Staph aureus and albus, nonhemolyt strep
	Throat	6	Staph albus, nonhemolyt strep, diphtheroids
	Wound of thigh	PM	B pyocyaneus, B subtilis, diphtheroids, nonhemolyt strep, anaerobic Staph albus
	Tonsil	PM	Diphtheroids (nonvirulent), micrococcus, Staph albus
24	Lung	PM	Nonhemolyt strep, Staph aureus
28	Stool	4	Neg for typhoid, dysentery organisms, parasites and ova
33	Sputum	6	Predominating H influenzae, many colonies D pneumoniae
34	Throat	10	Staph aureus
	Ulcer of left leg	PM	Staph aureus
38	Sputum	—	Nonhemolyt strep and staph
43	Intestines	PM	E coli and Aerobacter aerogenes
44	Skin lesion	17	Neg for C diphtheriae
	Throat	19	Neg for C diphtheriae and hemolyt strep
50	Throat	18	Nonhemolyt strep
	Lung	PM	Nonhemolyt Staph albus, Strep viridans (alpha prime), hemolyt Staph aureus

the majority a decided fluctuation in total protein, the most striking rise being from 38.5 to 144.2 mg per cent in 8 days, and the greatest fall being from 263

to 120 mg. per cent in 18 days. Instances in which the spinal fluid protein rose from normal to abnormally high levels in the course of the disorder are indicated in figure 1.

Leukocytes in this series varied from 0 to 110 cells per c mm. of spinal fluid, but generally were sparse, exceeding 20 in only 5 instances (cases 1, 4, 19, 34 and 48). Virtually all were lymphocytes, although in 1 instance there were 10 per cent neutrophilic leukocytes (case 1). A similar percentage of neutrophils was noted by Collier (43) in 2 cases in which there were 140 and 146 cells per c mm. of fluid. In a case described by Walter (219) in which 92 cells per c mm. were present, 50 per cent were neutrophils. Sometimes neutrophils predominated over lymphocytes, de Morsier and Steinmann (56) having observed in a case in which 82 cells were present that 60 per cent were neutrophils, and Johnson (107), in the presence of 47 cells, that 76 per cent were neutrophils.

Xanthochromia of the spinal fluid was not observed in any of our cases. It was noted in 22 per cent of the 18 cases of Dempsey, Karnosh and Gardner (57), and in 37 per cent of the 30 cases of Merritt and Fremont-Smith (138).

Colloidal gold studies were made on 22 of the series. In 10 the curves were in the normal range, in 4 there was a midzonal rise (e.g., 0134320000 in case 1), and in the remaining 8 the curves were of the first-zone type (e.g., 5554432100 in case 38). In one instance in which the illness lasted 46 days, the curves on the eighth, eighteenth and twenty-sixth days were all of the first-zone type (case 50). An analysis of all the cases in which colloidal gold studies were done revealed no correlation between the type of curve and the severity or duration of the disorder.

The sugar content of spinal fluid, as determined in 15 cases, varied from 57 to 182 per cent. It was 80 mg. per cent or lower in 8, 56.6 mg. per cent being the lowest (case 15), and higher than this value in 7: 87 (case 23), 90 (case 38), 92 (case 50), 98 falling to 85 (case 36), 100 rising to 182 (case 33), 107 (case 25), and 121 mg. per cent (case 32). Biernard (20) has observed a fall as low as 30 mg. per cent when evidence of meningeal involvement existed and a return to 76 mg. per cent after improvement had set in. Decreased spinal fluid sugar has been reported also by others (28, 171, 201). Sugar determinations carried out in 14 cases by Forster, Brown and Merritt (72) revealed a fall in 1 (39 mg. per cent), a slight rise in 4 (168 mg. per cent being the highest), and normal values in the remaining 9.

Spinal fluid chloride determinations yielded 627 mg. per cent (case 5), 695 rising to 717 (case 33), 700 (case 49), and 800 (case 23). Values in 13 cases of Forster, Brown and Merritt (72) were as follows: slight decrease in 4 (666 mg. per cent being the lowest), slight increase in 3 (768 mg. per cent the highest), and normal in the remaining 6.

C Blood Constituents

Hemoglobin and erythrocytes generally were within normal limits. Total and differential leukocyte counts were available in 33 cases, excluding the 2 associated with infectious mononucleosis. Mild to marked leukocytosis was

generally observed on admission to hospital irrespective of preceding upper respiratory infections. Relative and absolute increase of neutrophilic leukocytes was observed in 17, and of lymphocytes in 12. In the latter group the total number of lymphocytes per mm³ of blood varied from 3,900 to 8,281 and the percentage from 25 to 80 (table 6). Approximately one-fourth of the cases, therefore, were characterized by a relative and absolute increase in blood lymphocytes. Terminal leukocytosis with relative and absolute increase in neutrophils, regarded largely as a reaction to bronchopneumonia, was present in the majority of cases in which the data were available.

TABLE 6

Blood counts in twelve cases of fatal Landry Guillain Barré syndrome in which a relative and absolute increase in lymphocytes was observed

(+ signifies positive, 0, negative, and —, information not available)

CASE NO	DURATION	UPPER RESP INFECT	INITIAL TEMP AFTER ONSET	DAY AFTER ONSET COUNT DONE	LEUKOCYTES	NEUTROPHILS	LYMPHOCYTES	MONOCYTES	ENLARGED SUBCUTANEOUS LYMPH NODES	WT OF SPLEEN
	days		F		mm ³	per cent	per cent	per cent		gm
6	4	+	100.3	1	16,800	65	34	1	—*	300
9	4	+	98.0	1	22,300	75	25	0	—	175
11	5	—	98.0	2	10,000	59	39	2	0	150*
12	5	—	98.0	4	20,900	64	35	0	+	224
18	6	—	—	1	15,200	57	42	1	0	170
24	8	+	98.0	2	12,500	65	35	0	0	170
28	10	—	98.2	2	17,500	35	56	4	0	210*
36	12	—	98.0	5	16,900	51	49	0	0	230
40	14	—	98.6	7	7,800	42	52	2	+	240
41	15	+	98.6	2	7,600	20	80	0	0	250
47	29	—	98.6	1	17,200	70	30	0	0	110
48	33	+	98.6	1	8,000	25	67	0	0	200

* Pathologic changes suggestive of those seen in infectious mononucleosis were observed in the lymph nodes in Case 6, and in the spleen in Cases 11 and 28. In 4 other cases in which similar changes were present, the lymphocyte count was relatively normal.

Sedimentation of erythrocytes was studied in 10 cases. In 7 the values were greater than normal, 15 to 20 mm per hour being regarded as the upper limit of normal. As the disorder progressed, the sedimentation rate tended to rise, e.g., from 12 to 22 (case 28), 14 to 53 (case 44), 15 to 45 (case 32), and 31 to 35 mm in one hour (case 47). Stearns and Harris (193) have reported values of 20 to 24 mm sedimentation in one hour in 2 nonfatal cases of the disorder, and Bridgen (26), also in a nonfatal case, a value of 73 mm in one hour at the height of the illness, with a subsequent fall to 56 mm, and then to 12 mm.

D Other Data

Nonprotein nitrogen studies were performed in 6 cases. Values in excess of normal were obtained in 2. 32 and 66 mg per cent of serum in cases 50 and 45.

respectively Albuminuria with or without casts was noted in 3 (cases 6, 14 and 49), in case 6 the urine contained 3+ albumin, granular casts, and a few pus cells

Determinations of the concentration of chlorides in the plasma in 4 cases was found to be reduced in 3, the values being 356, 356 and 363 mg per cent respectively (cases 28, 40 and 50)

The heterophile antibody test, performed only in case 4, was positive in a dilution of 1:1792 In 6 instances reported by Baker (10) the heterophile antibody titre was 1.56 in 4, 1.112 in 1, and 1.224 in 1, and in 2 reported by Parker and Adams (149) the titre was negative in 1 and 1.64 in the other

Wassermann and Kahn tests were negative in all cases

V REVIEW OF THE LITERATURE OF PATHOLOGIC CHANGES IN THE LANDRY-GUILLAIN-BARRÉ SYNDROME

A *Nervous System*

1 *Introduction* A great disparity in observations marked the earlier attempts to determine the pathologic basis of the disorder under discussion Eichhorst (64) and Dejerne and Goetz (52), in 1876, and Van den Velden (209), in 1877, described degenerative changes in the more proximal part of the peripheral nervous system, and in the ensuing years these observations were well substantiated (22, 66, 102, 104, 140, 144, 165) Degenerative changes restricted to the distal ends of the nerves in a case of 23 days' duration were noted by Rolly (172), and solely in the peripheral nerves by Dejerne (51) in 2 cases of unstated duration On the basis of his observation, Rolly advanced the view that the disorder starts peripherally and ascends nerves Duménil (60, 61) was the first to demonstrate such a mode of spread in his classic work on the subject, but his case was of 5 months' duration In this connection it is worthy of note that Marinesco (133) on examining the skin in 1 case of the disorder, observed advanced proliferative changes in Pacinian and Meissner's corpuscles as well as complete degeneration of their emergent fibers Walter (219), Margulis (130), and others have observed that the most marked changes occur in the spinal nerves, i e, in the region where the anterior and posterior roots join, and extend both proximally and distally to a varying degree Brussilowski (30) noted that nerve fibers in roots were not affected in their entire extent but in focal areas, the intervening parts of the nerve fibers being normal

The central nervous system also was implicated by some earlier workers Chalvet (39) was among the first to describe swelling and other degenerative changes in anterior horn cells Hoffmann (102) reported severe swelling and disintegration of myelin in the pyramidal tracts of the medulla oblongata and spinal cord, and in the intramedullary part of the anterior spinal roots, he also observed scattered small perivascular collections of lymphocytes in the roots Wood and Dercum (225) noted diffuse myelin degeneration in the spinal cord In a review of the pathologic changes observed in "Landry's paralysis" up to 1904, Schmaus (182) listed some 14 instances in which degenerative changes in the proximal part of the peripheral nervous system, occasionally accompanied by

inflammatory cells, were observed, and similar changes in the spinal cord or medulla oblongata, or both, in 11

2 Peripheral Nervous System In the more recent reports of the pathology of this disorder there is agreement that the changes found most consistently are in the more proximal part of the peripheral nervous system, and that they include vascular engorgement, edema, degeneration of myelin and axon cylinders with phagocytosis of the debris by histiocytes, and proliferation of the cells of Schwann. Inflammatory cells, usually lymphocytes, have been found in affected portions of the peripheral nervous system, usually the roots, and not infrequently in the dorsal root ganglia (sometimes predominantly in the ganglia), at various stages of evolution of the disorder—5 days (8), 6 and 7 days (157), 7 days (55), 8 days (122), 12 days (5, 22, 54), 15 days (204), 18 days (31), 3 weeks (76, 130, 148, 155), 6 weeks (56, 106, 109, 113, 115, 153), 9 weeks (82), 12 weeks (2, 112), and 17 weeks (134). The infrequent occurrence of inflammatory cells in cases of brief duration has been taken as evidence that the presence of such cells in cases of longer duration constitutes a response to neuronal damage, not an integral part of the initial process. Gutner (76), in describing a case of polyneuroradiculitis ascendens (Landry's paralysis) which ended fatally after 3 weeks of illness, and in which degenerative changes and inflammatory cells were found in the nerve roots, stated "Wir müssen uns also, wenn wir von Radiculitis sprechen darüber klar sein, dass wir den teilweise hochgradigen Infiltrate eine reparatorische Entzündung in Sinne von Aschoff vor uns haben." Pette and Korney (157), on the other hand, expressed the view that a lymphocytic exudate may be taken as evidence of virus origin, and that a purely degenerative process indicates a toxic agent, accordingly they classified Landry's paralysis etiologically into two forms, virus and toxic.

3 Central Nervous System Changes in the central nervous system also have been observed, particularly when the disorder has run a relatively long course, diffuse myelin degeneration in the spinal cord (30, 122) and also in the lower brain stem (127) (best brought out by the Marchi method), degeneration or phagocytosis in both in the posterior columns of the spinal cord (28, 82, 178, 187) and in the dorsal spinocerebellar tracts (1, 187), an increase of round cells or glia in the grey matter of the spinal cord (25, 30, 34, 35, 124), sparse perivascular collections of lymphocytes in the brain (28, 86, 153, 155, 157), sparse, diffuse, patchy demyelination with histiocytic reaction, mainly perivascular, in the cerebral white matter and cortex (10, 162), proliferation of marginal glia of the cerebral cortex and chronic cell changes in cortical laminae (124), chromatolysis of Betz cells (103, 106, 115), and early neuronophagia of Betz cells (30) and of pyramidal cells of the hippocampus (28). The majority of workers, however, have observed no abnormalities in the central nervous system aside from degenerative changes, usually minor, in anterior horns and cranial nerve nuclei. Several writers have laid stress on such changes (30, 32, 33, 80, 85, 86, 116, 136, 179, 205). Some believed that the changes in motor nuclei were primary, and others that they represented retrograde degeneration. Brissilowski (30), who observed degenerative changes in roots and anterior horn cells, expressed the opinion that the changes were independent of each other.

4 *Leptomeninges* The spinal leptomeninges also participate in the pathologic process in some cases, to judge from 1) hyperemia, swelling and thickening of the spinal arachnoidal trabeculae (35), 2) proliferation of the arachnoid (so severe as to lead to spinal or posterior fossa block [17, 20, 91] and necessitate exploratory operation [71, 124, 135]), 3) slight cellular reaction and infiltration of the cerebral leptomeninges (28, 173), 4) mild lymphocytosis of the leptomeninges of the spinal cord adjacent to the spinal roots, at times continuous perivascularly into the periphery of the spinal cord (55, 104, 122, 132, 133, 134, 153, 157), and 5) the presence of small groups of leukocytes in the cerebral leptomeninges (34)

5 *Comment* Much has been made of the lack of pathologic changes in the peripheral and central nervous systems in some cases of Landry's paralysis, and indeed some authors have asserted that only when abnormalities are lacking is the diagnosis of Landry's paralysis warranted. Cattle (37), in 1909, expressed the then prevalent opinion "A certain mystery has always hung over Landry's paralysis because it has so frequently happened that no morbid changes in the nervous system have been discovered after death," but added, as the result of personal observations, "the notion that Landry's paralysis is associated with no morbid tissue changes of permanent character can no longer be maintained." Similarly, Mills and Spiller (140), in reviewing the pathologic findings in numerous cases of Landry's paralysis, remarked "A total of twenty-eight recorded cases in which lesions were found must make us skeptical toward the report of those cases in which no lesions were noted." It is commonly recognized that a few days are required before changes in the nervous system become apparent. Should death occur before this time, the nervous system would be expected to be free from abnormalities, a view well expressed by Soltmann (190) "Je acuter der Verlauf um so weniger wird man irgend wie anatomische Veränderungen erwarten dürfen, der Kianke stirbt, ehe es zu solchen kommen konnte, bei subacutem Verlauf werden sich die Erscheinungen der Polyneuritis klinisch und anatomisch decken, und bei protahierten Nature im Rückenmark, in der grauen Vorderesäule, multipolar Ganglionzellen eventuell in den Seitenstränge hervortreten können."

B Other Tissues

The literature contains relatively few accounts of careful studies of the thoracic and abdominal viscera in the disorder under discussion. Enlargement of the spleen was remarked as early as 1867 by Oulmont and Hayem (147), and by many others after them. Increase in the size of lymph nodes has been observed fairly frequently since the 1860's. Bradford, Bashford and Wilson (25) found patchy parenchymatous and glomerular nephritis and degenerative changes in voluntary muscles, and slight and variable infiltration of round cells in the portal triads of the liver. Gartner (76) observed acute ileitis with reactive changes in the adjacent lymph nodes in 1 instance. Péhu and Dechaume (153) noted mild interstitial inflammatory reaction in skeletal and cardiac muscle in 1. Degenerative and/or inflammatory changes in skeletal muscle have been reported also by others (1, 23, 84, 147, 157, 174, 205, 215). Maimesco and Diaganescu (134) found perivascular and interstitial infiltrates in skeletal muscles and col-

lections of lymphocytes in the adrenal gland Sabin and Aving (179), in a study of 3 cases, reported cellular infiltrates and/or focal necroses of varying degrees in the heart, liver, adrenal glands, and kidneys, Aving (7) remarked that these are "changes which are considered to be secondary to most pathologists." In a highly unusual case of the disorder reported by Parker and Adams (149), the cellular infiltrate in viscera was even more striking.

VI. PATHOLOGIC OBSERVATIONS

A. Central Nervous System and Meninges

In our series, gross examination of the brains revealed only slight to moderate edema, and in 1 instance mild hemorrhage into the leptomeninges of the convex surface of the brain (case 1). The weight of the brains varied from 1250 to 1730 gm., and averaged 1493 gm.

On microscopic examination the brains showed little of significance. In some of the more fulminant cases there were edema and acute cell changes, and in approximately one fifth of the series small, sparse perivascular collections of lymphocytes which were predominantly in the white matter and subependymal tissue. Scattered petechiae in the central nervous system, particularly in the grey matter of the spinal cord, were observed in about one-third of the cases. In occasional instances, the leptomeninges, cerebral and spinal, contained petechial hemorrhages. Hypertrophy, and in some cases hyperplasia of fixed tissue cells of the intracranial and spinal leptomeninges occurred in 15 cases. An outstanding example is illustrated in figure 3A. Such proliferation was usually diffuse over a relatively small area, but sometimes was concentrated in the region of vessels. Proliferative arachnoiditis around the more distal parts of spinal roots occurred in a few cases, the most striking instance of which was case 34 (fig. 3B). Cellular infiltrate into the leptomeninges was observed in 4 instances (cases 19, 27, 30 and 44). The infiltrates were exceedingly small in 3 of these and were present in the anterior median fissure or on the ventral aspect of the spinal cord, in the other (case 30) it was more abundant, consisting of lymphocytes, large mononucleus, and scattered neutrophilic leukocytes, and was pocketed in the recess adjacent to a spinal root (fig. 3C). Engorgement of vessels of the leptomeninges and roots of the spinal cord was a common finding (fig. 4).

In the spinal cord in approximately 10 cases there was mild chromatolysis of anterior horn cells, in 3 others the degenerative changes were relatively severe (fig. 5). The hematoxylin and eosin, Masson trichrome, cresyl violet, and Spielmeier myelin sheath stains revealed that there was no cellular infiltrate or degenerative change in the spinal cord in any of these cases (aside from the chromatolysis mentioned). In only 1 instance, of 14 days' duration, did the Bodian activated silver method show only but definite degeneration of the axis cylinders traversing the anteromedian group of nerve cells (fig. 6A), the anterior roots displayed definite degenerative changes in many of their axis cylinders (fig. 6B) and myelin sheaths, also a few scattered macrophages, lymphocytes, and proliferated Schwann cells. Inasmuch as the anterior horn cells in this case were normal, it was concluded that the axis cylinder changes within the anterior

horn were the result of retrograde degeneration. The only other instance of degenerative change of axons within the spinal cord was case 28, of 10 days'

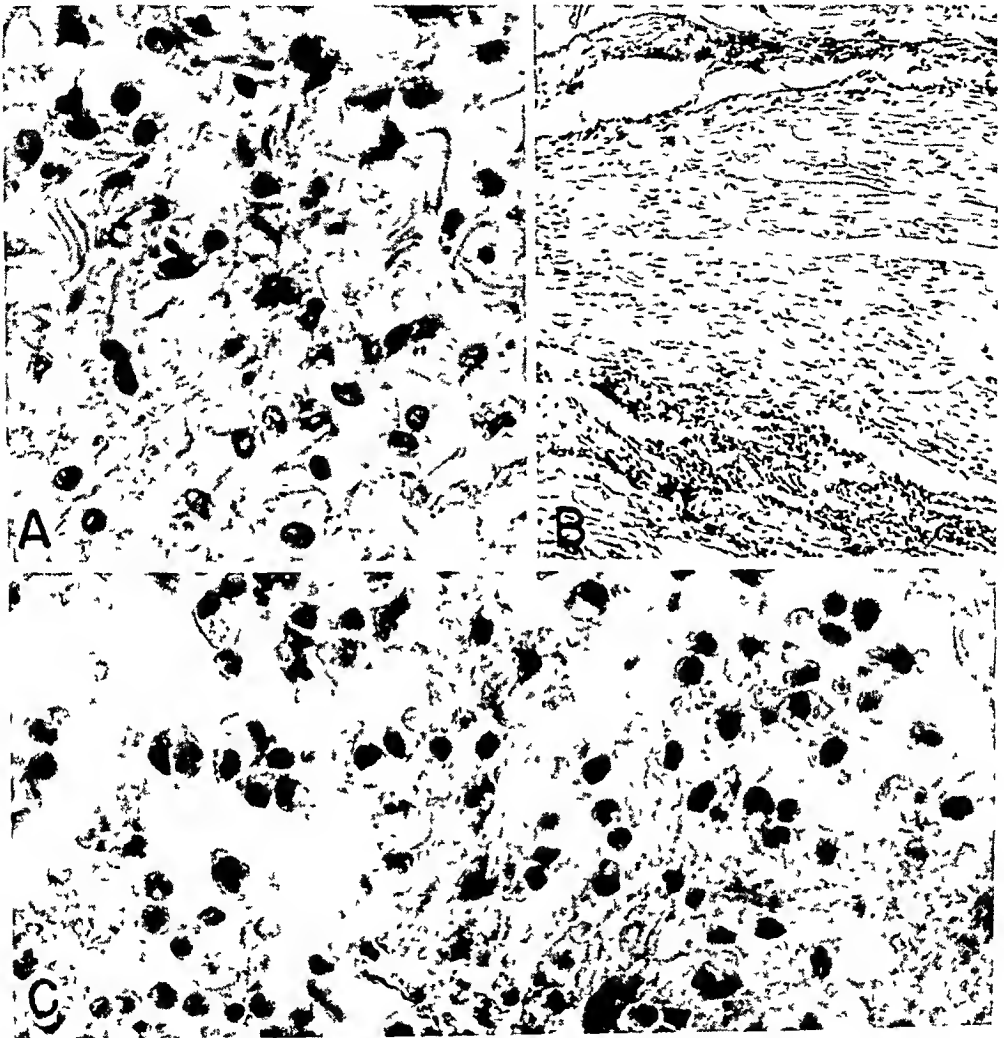


FIG 3 LEPTOMENINGEAL CHANGES

In A (case 29, duration 10 days), from the cerebral leptomeninges, the fixed tissue cells have proliferated, and some have been converted into free macrophages. Hematoxylin and eosin stain $\times 450$ (AIP Neg 98745). In B (case 34, duration 11 days), from the distal part of a spinal root in the lumbar region, there is an advanced focal proliferative meningoarthritis, the adjacent dura is free from change. (The spinal fluid in this case contained 30 cells per c mm on the day before death.) Cresyl violet stain $\times 85$ (AIP Neg 98935). In C (case 30, duration 10 days), from the leptomeninges in the vicinity of a spinal root in the lumbar region (circled in fig 13), there are numerous mononuclear cells and scattered neutrophilic leukocytes. (Spinal fluid study 8 days before death revealed 2 cells per mm³.) Hematoxylin and eosin stain $\times 500$ (AIP Neg 101673).

duration, in which Bodian activated silver preparations showed relatively severe swelling and distortion of axis cylinders in the immediate vicinity of the posterior horns.¹⁰

¹⁰ Since the completion of this study, the Army Institute of Pathology received a case of 77 days' duration in which the posterior columns showed demyelination with astrocytosis (AIP Acc 210103). Apparently more than 46 days and less than 77 days are required for degeneration to extend from the posterior roots into the posterior spinal columns.

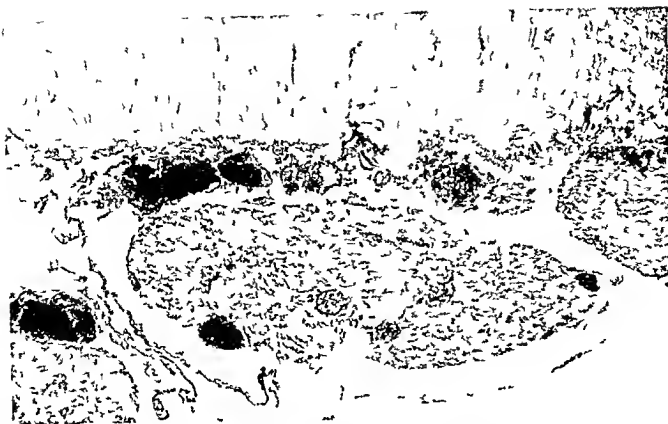


FIG 4 (CASE 21, DURATION 6 DAYS)

Extreme engorgement of vessels in leptomeninges and anterior roots. The section is from the uppermost thoracic region. (Scattered small perivascular hemorrhages were present in the spinal gray matter of this section.) Hematoxylin and eosin stain $\times 95$ (AIP Neg 95952)

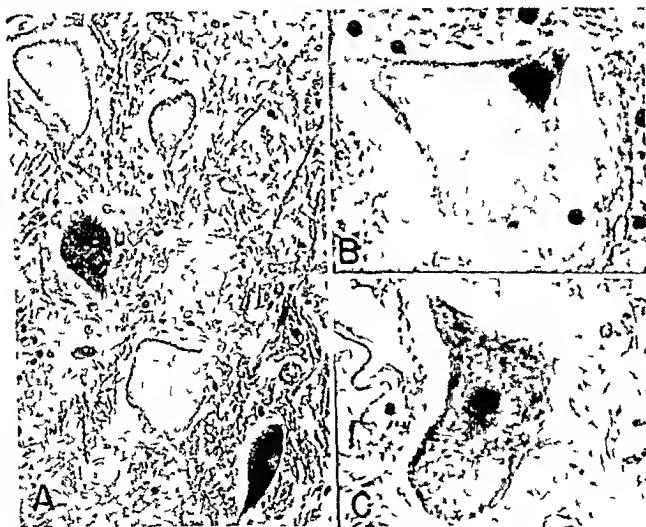


FIG 5 (CASE 23, DURATION 10 DAYS)

Degenerative changes in anterior horn cells. (Degenerative changes in the peripheral nervous system were well advanced in this case see fig 7C.) The section is from the upper sacral region. In A some of the cells are amorphous except for a rim of Nissl substance $\times 185$ (AIP Neg 101214). In B is illustrated a dislodgement of the nucleus into the most proximal part of cytoplasmic process $\times 400$ (AIP Neg 101212). In C, a large mass of perinuclear material, presumably increased lipochrome, is to be seen $\times 545$ (AIP Neg 101215). Masson trichrome stain.

B Peripheral Nervous System

1 *Spinal Nerves* The most profound alterations were encountered in the peripheral nervous system. The earliest change consisted of edema. It was



FIG. 6 (CASE 40, DURATION 14 DAYS)

In A, from the anteromedian cell group of the anterior horn of the lumbar cord, there is swelling, beading and fragmentation of axis cylinders. The nerve cells are normal. $\times 280$ (AIP Neg 85684). In B, from the most proximal part of the anterior root (same section as in A), the degenerative changes in axis cylinders are more pronounced and there is enlargement of fixed tissue cells. $\times 600$ (AIP Neg 85685). Bodian activated silver method.

present in a case in which the patient had died 4 days after the onset of symptoms (case 6). In this instance, edema was the only significant feature, although slight swelling and irregularity of the myelin sheaths were also observed. At the 5-day stage, myelin sheath and axis cylinder changes were readily visible (figs 7A and 7B). In none of the early cases was there any local cellular reaction or

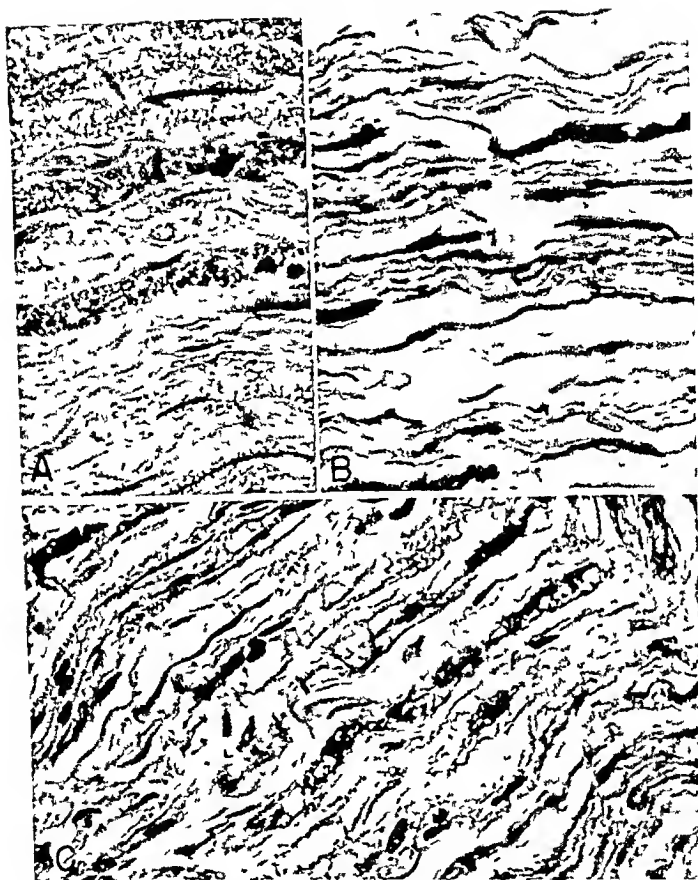


FIG 7 (CASE 11, DURATION 5 DAYS, AND CASE 28, DURATION 10 DAYS)

In A (case 11), from an unidentified spinal root the myelin is markedly fragmented Masson trichrome stain $\times 500$ (AIP Neg. 98928) In B, from the same case a few axon cylinders show swelling beading, and other distortions Bodin activated silver method $\times 550$ (AIP Neg 98752) In C (case 28) the section is from an upper lumbar root There is extensive degeneration of the axon cylinders with vacuolization and fragmentation of myelin Inflammatory reaction is absent and there is no proliferation of Schwann cells Bodin activated silver method $\times 600$ (AIP Neg. 85666)

inflammatory exudate At the 8 day stage, myelin and axon cylinders showed a greater degree of disintegration, and at 9 days scattered small groups of lymphocytes were occasionally observed At the 10 day stage, the changes in myelin and axon cylinders were still more marked (fig 7C), but activation of fixed tissue

cells and Schwann cells was still in abeyance. At 11 days, however, numerous phagocytes were encountered (fig 8A) (although in one instance they were present at 9 days, see fig 11A), and there was early activation and suggestive proliferation of Schwann cells, also there was a somewhat greater number of

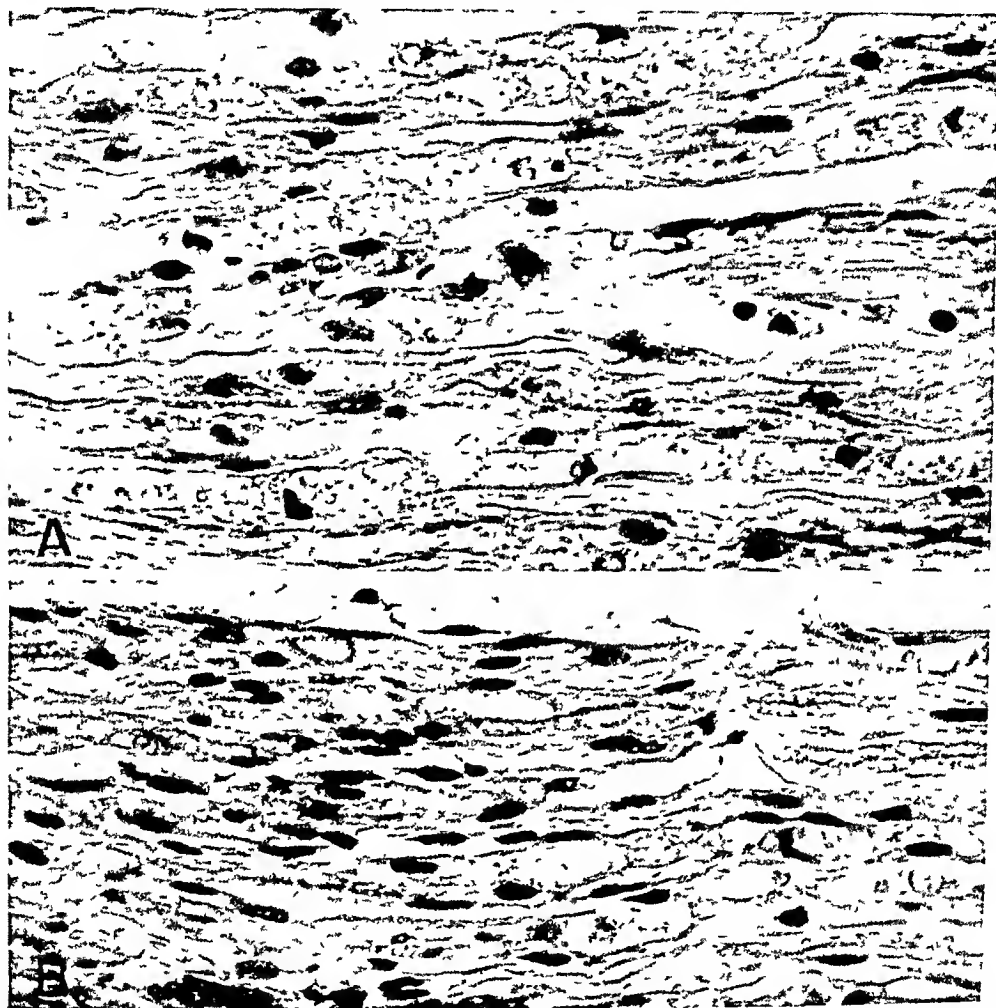


FIG 8 THE STAGES AT WHICH MACROPHAGES AND PROLIFERATED SCHWANN CELLS USUALLY BECOME EVIDENT

In A (case 34, duration 11 days), from the same specimen as illustrated in fig 3B, degeneration of myelin and axis cylinders is well advanced and numerous macrophages occupy Schwann tubules. Masson trichrome stain $\times 500$ (AIP Neg 103477). In B (case 38, duration 13 days), from the sciatic nerve, Schwann cells have begun to proliferate. Hematoxylin and eosin stain $\times 350$ (AIP Neg 103478).

lymphocytes scattered diffusely through the nerve bundles. At 13 days, Schwann cell proliferation, in some regions focal and in others diffuse, was clearly evident (fig 8B).

After the 13-day stage, the changes recounted were met with consistently but they varied in degree in different parts of the peripheral nervous system. In 1 instance, of 23 days' duration, an intercostal nerve was severely degenerated and its component nerve fibers widely separated by coagulated amorphous material

(figs 9A and 9B), also in this case there were the customary degenerative changes and a scattering of lymphocytes in spinal roots and peripheral nerves (fig 9C)

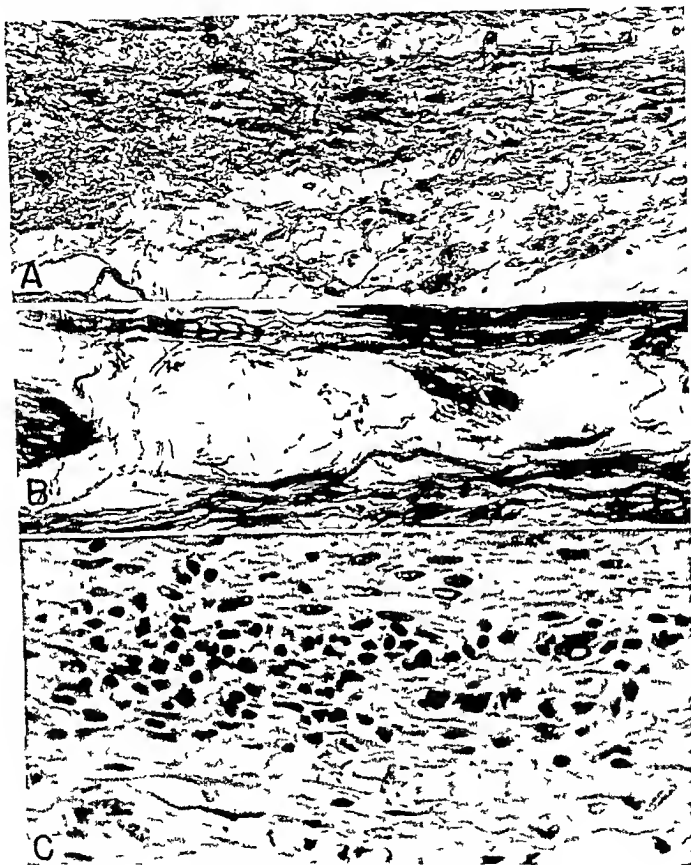


FIG 9 (CASE 43, DURATION 21 DAYS)

In A, from an intercostal nerve, the nerve bundles are degenerated and disrupted by edema fluid and endoneurial fibrosis has occurred (Masson trichrome stain $\times 35$ (AIP Neg. 102021)). In B, from a field in A, the degenerative changes edema fluid, and endoneurial fibrosis are shown to better advantage. One nerve fiber is visible $\times 360$ (AIP Neg. 102017). In C, also from an intercostal nerve, there are macrophages within Schwann tubules, proliferated Schwann cells and lymphocytes (Hematoxylin and eosin stain $\times 400$ (AIP Neg. 101760)).

The most severe changes were noted in the case of longest duration, namely 46 days. There was marked edema of the nerve sheaths, which was out of

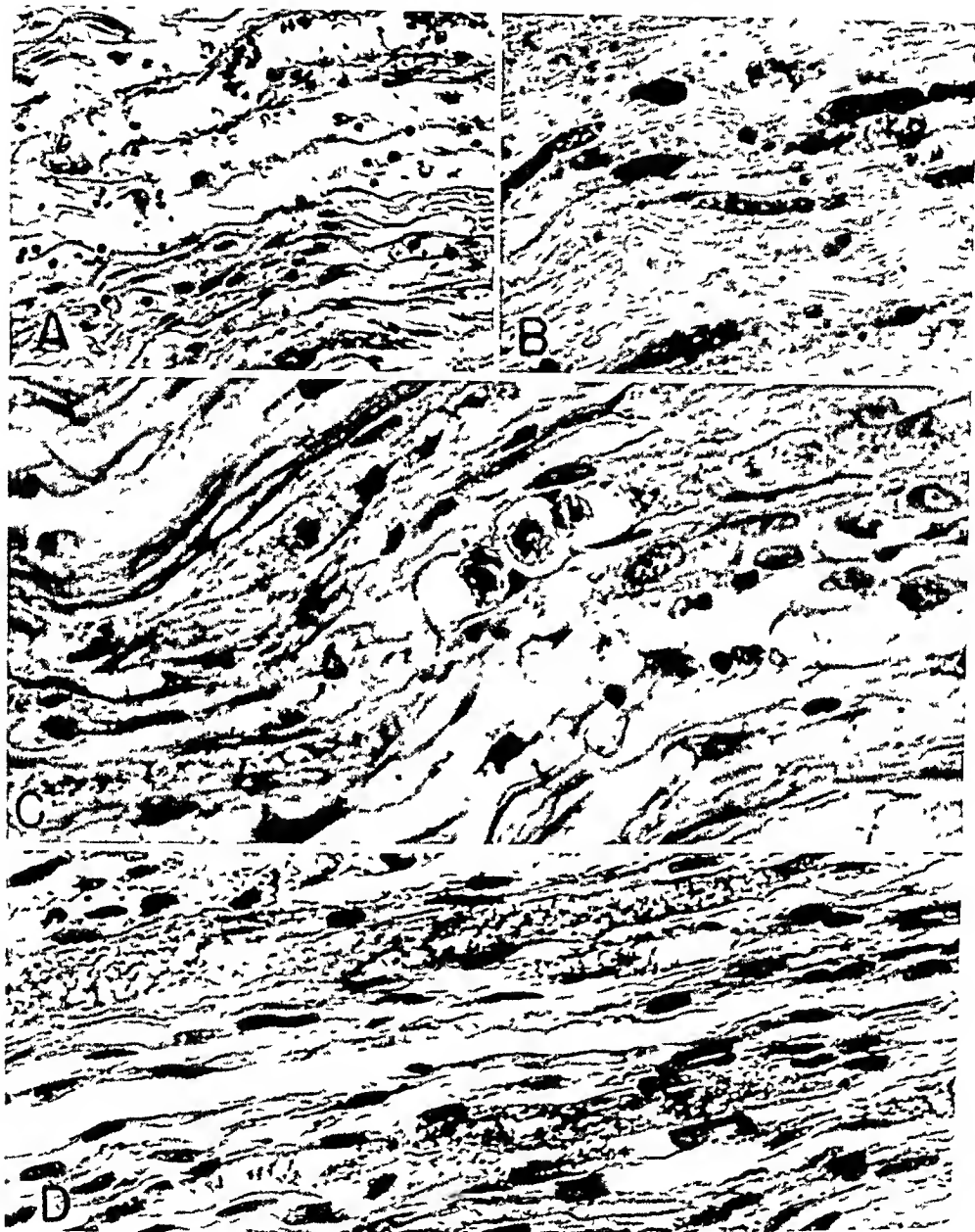


FIG 10 (CASE 50, DURATION 46 DAYS)

Changes in a peripheral nerve (sciatic or femoral) In A, myelin and axis cylinders have disappeared and there is severe edema and a scattering of lymphocytes and macrophages. Occasional proliferated Schwann cells are to be noted. Hematoxylin and eosin stain $\times 230$ (AIP Neg 85675). In B, most of the myelin that remains is fragmented and disintegrated. Spilmeyer modification of the Weigert myelin stain $\times 230$ (AIP Neg 85678). In C, there is marked edema and complete degeneration of axis cylinders. Phagocytes occupy Schwann tubules, and some of them contain remnants of axis cylinders. Bodian activated silver method $\times 600$ (AIP Neg 95673). In D, most of the myelin sheaths are degenerated and Schwann cells have undergone marked proliferation. Slight edema is present, but there are no inflammatory cells. Masson trichrome stain $\times 500$ (AIP Neg 85677).

proportion to the cellular reaction (fig 10A). In many regions scarcely a normal myelin sheath remained (fig 10B). Debris of broken-down myelin and macrophages containing small fragments of nondegenerated myelin and droplets of

lipoid were abundant (fig 10C). In some sections stained by the Bodian activated silver method, not a single normal axis cylinder was encountered, all that remained of nerve bundles being a few small broken fragments of axis cylinders and empty sheaths and their connective tissue coverings (figs 10A and 10C). Proliferation of Schwann cells was evident in some regions (fig 10D), but not in others. Occasional groups of Schwann cells undergoing mitosis also were noted. In only an occasional section was a sparse scattering of lymphocytes observed.

In the series as a whole, the changes were usually most prominent in the region where the motor and sensory roots join to form the spinal nerve. They occurred to a diminishing degree in the adjacent parts of the spinal roots, especially the anterior roots, and seldom reached the most proximal portion of the roots. The degree of change diminished also in the peripheral nerves as one proceeded distally from the spinal nerves, but there was insufficient material to determine how far distally the lesions extended, or indeed the relative severity of involvement of spinal nerves and peripheral nerves. In cases of short duration degenerative changes were decidedly focal in character, sometimes the foci were large, presenting a leopard skin effect in the section as a whole, and occasionally a single axis cylinder and its myelin sheath were severely degenerated while the immediately adjacent fibers were of normal appearance. Nerve fibers close to vessels or to the pia suffered no more than those distant from these structures. Even in cases of longer standing the changes were not universal in a root or peripheral nerve, but usually varied in severity from fascicle to fascicle in the same nerve trunk. Vessel walls usually were unaffected, but in an occasional case, especially of longer standing, vessels here and there showed proliferation of endothelial cells and adventitial histiocytes. This was a striking feature in a case of 8 days' duration studied after this report was prepared (AIP Acc 203980). The patient had had severe alcoholism. Scattered among the proliferated adventitial histiocytes were small round cells resembling lymphocytes, and there were occasional neutrophilic leukocytes. Perivascular nerve fibers were damaged, but no more so than fibers at a distance from vessels.

Evidence of degeneration in dorsal root ganglia varied greatly from case to case and even from one ganglion to another in the same case, however, mild to marked chromatolysis was present in most ganglia. In some there were small numbers of lymphocytes but no neutrophilic leukocytes. In several cases a focal proliferation of the endocapsular cells was noted. Occasionally this was well marked, but usually it was mild. It seemed to us that this endocapsular proliferation was secondary to the degeneration of the nerve cells, since it did not, as a rule, correspond to the degree of proliferation of the Schwann cells of the spinal nerves and since it was just as prominent in chronic as in acute cases.

2 Sympathetic Nervous System Sympathetic ganglia and nerves were available in only a few cases. In only one were changes observed, and then in the superior cervical sympathetic ganglion there was edema and a slight excess of small round cells, apparently lymphocytes, in the interstitium, with an occasional grouping of such cells around blood vessels, capsular cells had not proliferated (case 50).

3 Cranial Nerves What has been related of the changes in the spinal periph-

eral nervous system was true also of the cranial nerves, both as regards the nature of the lesions and the time at which they became apparent (fig 11)



FIG 11 CHANGES IN THE VTH CRANIAL NERVE

In A (case 27, duration 9 days), axon cylinders are in various stages of degeneration, myelin is disintegrated, and Schwann tubules are filled with macrophages. A few Schwann cells show evidence of activation. (In this case numbness of the face, mouth and teeth was the leading symptom.) Bodian activated silver method $\times 235$ (AIP Neg 101775). In B (case 44, duration 22 days), most of the Schwann tubules are filled with macrophages. The remaining myelin sheaths show disintegrative changes. Schwann cells have not proliferated and inflammatory exudate is absent. (Involvement of the Vth nerve was not detected clinically.) Masson trichrome stain $\times 425$ (AIP Neg 101764).

The lesions generally reached to within a short distance of the brain stem. The gasserian ganglion in 1 instance showed moderate proliferation of endocapsular cells (case 38).

4 *Findings in Different Clinical Syndromes* An especial effort was made to

determine whether there were any distinguishing pathologic features in the 4 cases in which sensory disturbances were lacking. In one of these (case 8), of 4 days' duration, there was the characteristic engorgement of leptomeningeal and radicular vessels and edema of the spinal roots, also there were a few petechiae in the anterior horns of the spinal cord. In another (case 14), of 5 days' duration, engorgement of vessels and petechial hemorrhages in anterior horns were also observed. An occasional anterior horn cell showed slight degenerative change, while axis cylinders in the anterior root component of the spinal nerve were swollen and displayed other distortions (fig 12), and the myelin in this region was beginning to undergo fragmentation, the corresponding part of the posterior root was free from change but there were occasional swollen and beaded axis cylinders in the most distal part of the posterior root ganglion.



FIG. 12 (CASE 14, DURATION 5 DAYS)

In the region of fusion of anterior and posterior roots, there are swelling and other distortions of the axis cylinders of the anterior root component (in lower one third of photograph) and a lack of such changes in the posterior root component. The leptomeninges are free from change. Bodian activated silver method. $\times 55$ (AIP Neg. 103487).

In still another (case 22), of 6 days' duration, the material was not available for study. And in the fourth (case 25), of 8 days' duration, the VIIth nerve showed the changes anticipated at this stage, but satisfactory spinal root material was not available for study. The observations in the second case, at least, if a single sampling is to be considered representative, would serve to explain motor paralysis in the absence of sensory disturbances, had the changes in the fibers in the posterior root ganglion progressed further it appears likely that alterations in sensibility would have developed. An effort was also made to determine the basis of the anesthesia which formed such a striking part of the clinical picture in a few of the cases. In such cases it could generally be established that the anterior and posterior roots were similarly affected. Thus, in case 30, of 10



FIG 13 (CASE 30, DURATION 10 DAYS)

Degenerative changes in anterior and posterior roots in the presence of widespread paralysis and anesthesia. In A are illustrated the roots as they penetrate the dura. The squares indicate the approximate regions from which photographs B and C were taken (The leptomeningeal exudate enclosed in the circle is illustrated in fig 3C.) Masson trichrome stain $\times 22$ (AIP Neg 103817.) In B and C it will be noted that axon cylinders are severely degenerated. Macrophages are not present, nor have Schwann cells proliferated. Bodian activated silver method $\times 235$ (AIP Negs 103759 and 103761.)

days' duration, degenerative changes in axon cylinders were found in both roots, particularly near their region of fusion (fig 13), in this case, as already men-

tioned, there were degenerative changes in axis cylinders of the posterior and lateral columns of the spinal cord, but ganglion cells of the cord were intact¹¹

C Other Tissues

The most striking change in the viscera was that of bronchopneumonia, which was found in 33 cases. It usually was early and hypostatic in form. Occasionally it was of the aspiration type. Congestion and edema of the lungs prevailed in the majority. Of the 50 cases there was an excess of fluid in the pleural space in 9, and in the pericardial sac in 14, the greatest amount of pleural fluid being 500 cc (case 10), and of pericardial fluid 100 cc (case 44). Low grade in-

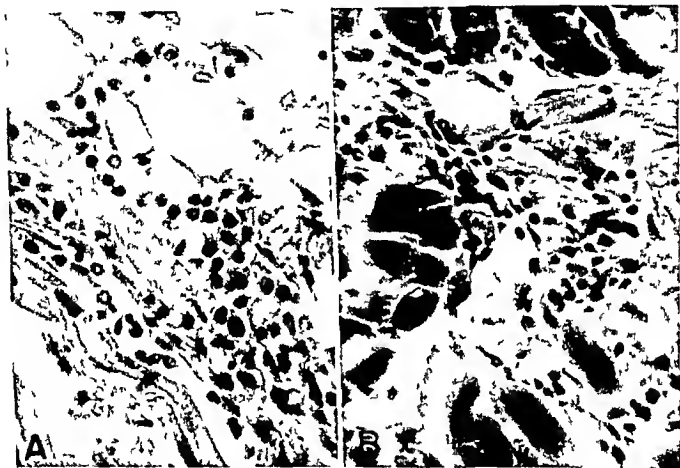


FIG. 14 FOCAL MYOCARDITIS

In A (case 23, duration 8 days) lymphocytes and large mononuclear cells predominate $\times 450$ (AIP Neg 100888). In B (case 29, duration 10 days) there are also a few Anitschkow cells $\times 400$ (AIP Neg 93938). Hematoxylin and eosin stain.

terstitial pneumonitis was noted in 1 instance (case 24). In another, the lungs were the seat of subacute miliary tuberculosis, in addition there were tubercles in the liver and spleen and a tuberculous perisplenitis (case 3).

The heart appeared normal in all except 7 cases in which mild focal myocarditis was observed (cases 14, 18, 27, 28, 29, 34 and 44). Such foci, invariably small and sparse, consisted of perivascular collections of lymphocytes, macrophages, and Anitschkow cells (fig. 14). Collections of lymphocytes were found occasionally in the epicardium, especially around the coronary vessels (cases 23, 29, 32, 42 and 45).

¹¹ The pathologic changes in the nervous system and viscera in the 2 cases of proven infectious mononucleosis in our series (cases 4 and 5), have been reported by Ricker et al (167).

The spleen¹² was available for study in 43 of the cases, exclusive of 2 associated with infectious mononucleosis (cases 4 and 5) and 1 which was tuberculous (case 3). The weight of the spleen varied from 60 to 424 gm, and in 17 was 200 gm or more. The splenic weight was 300 gm or more in cases 3, 6, 27, 30 and 37. The mean weight was 186 gm. The weights bore no significant relation to the length of illness, but tended to be more in the range of normal the longer the duration, in the 10 cases of longest duration, for instance, the spleen weighed from 60 to 120 gm in 4, from 120 to 160 in 2, and from 160 to 200 in 2, and from 200 to 250 in 2. Microscopically, the splenic pulp was generally the seat of intense congestion. In some spleens the pulp appeared hyperplastic, and in others the follicles. In 6 there were reactive changes in the pulp, capsule, trabeculae, adventitia of arteries, and adventitia and subintima of veins, in varying combinations, suggestive of those seen in infectious mononucleosis (46, 189) (cases 1, 13, 25, 28, 34 and 38), the atypical lymphocytes seen in these regions resembled those of frank infectious mononucleosis but were fewer (fig 15).

The lymph nodes were but little affected. Cervical lymph nodes were slightly to moderately enlarged in 10 cases (excluding the 2 associated with infectious mononucleosis), but tended to recede as the illness ran its course. Generalized slight lymphadenopathy was noted clinically in 1 of these, but at autopsy the nodes were no longer enlarged (case 43). Associated enlargement of axillary nodes was observed in 2 (cases 23 and 46). Mesenteric lymph nodes were increased in size in only 2 instances (cases 15 and 44), and mediastinal nodes in 1 (case 3). Microscopically, there was inconstant and generally mild reaction on the part of the lymphocytes and reticuloendothelial cells. In only 1 instance were there changes suggestive of those seen in infectious mononucleosis (case 6).

The liver showed focal necrosis with intralobular accumulations of lymphocytes in 2 instances, of slight to moderate degree in 1 (case 10) and inconsequential in the other. An increase in periportal lymphocytes was noted in case 25. Chronic hepatic cirrhosis was observed in case 30, in which there had been a history of alcoholism. Subacute hepatitis of moderately advanced degree was observed in case 37, a finding which confirmed the clinical impression.

The gastrointestinal tract exhibited little of significance. There was hyperplasia of lymphoid elements of the ileum in 1 (case 1), chronic enteritis in 1 (case 19), chronic gastritis in 1 (case 46), and volvulus of the small intestine in 1 (case 32).

The kidneys were of normal appearance in the great majority of cases. Congestion was frequently conspicuous. Lower nephron nephrosis was present in 3 instances (cases 6, 23 and 50), and changes suggestive of this condition in 5 others (cases 1, 14, 27, 28 and 47). Sulfonamides or transfusions had been administered in 3 of these (cases 6, 28 and 47).

The adrenal glands were normal except for focal cortical necrosis with lymphocytic exudate in 1 (fig 16). Also there were occasional small collections of lymphocytes in the zona fasciculata in 2 (cases 45 and 48) and at the cortico-

¹² Study of the spleen, lymph nodes, bone marrow and blood picture in this series was carried out in collaboration with Dr R Philip Custer.



FIG 15 CHANGES IN THE SPLEEN

In A (case 28, duration 10 days), there is a subendothelial lymphocytic reaction in a large vein. (A similar change was present beneath the intima and in the adventitia of several intratrabecular arteries, as well as in the capsule and trabeculae.) This type of reaction is noted consistently in infectious mononucleosis, although it is not necessarily pathognomonic of that disease $\times 285$ (AIP Neg. 102188). In B (case 34, duration 11 days) a subendothelial lymphocytic reaction similar to that shown in A is to be seen $\times 550$ (AIP Neg. 102519). In C (case 28, duration 10 days), the pulp displays marked lymphoid hyperplasia, and there is a scattering of atypical lymphocytes similar to those of infectious mononucleosis $\times 650$ (AIP Neg. 102189). Hematoxylin and eosin stain.

medullary junction in 2 (cases 28 and 46). It is recognized that this type of lymphocytic reaction in the adrenals is commonly observed in any series of unselected autopsies. An occasional small perivascular collection of lymphocytes

was noted in the periadrenal tissue in 1 instance (case 29), and periadrenal hemorrhage in 5

The bone marrow showed nothing of significance aside from occasional minor granulocytic hyperplasia.

Skeletal muscle was available for study in 13 cases. In 7 it was normal, in 1 there was spotty swelling of muscle fibers (case 13), in 3 mild degenerative changes with scanty proliferation of sarcolemmal cells (cases 8, 30 and 47), in 1 moderate necrosis with proliferative changes (case 41), and in 1 severe changes



FIG 16 (CASE 48, DURATION 33 DAYS)

The cortex of the adrenal gland is edematous and there is irregular necrosis, also there are infiltrates of small round cells. (The remainder of the cortex was edematous but was otherwise normal.) Hematoxylin and eosin stain $\times 75$ (AIP Neg 103475)

(case 6) In the latter, only a few muscle fibers retained their striations, while most showed swelling, clumping, fragmentation, and vacuolization (fig 17A), all muscles available displayed the same changes. The acuteness of the process was indicated by the presence of neutrophilic leukocytes around some of the disintegrating muscle fibers. The blood vessels supplying these muscles were normal. The example of necrosis of lesser scope is illustrated in Fig 17B.

The only other pathologic change seen was embryonal carcinoma of the testis in case 8. In this instance the patient had been admitted to hospital with a swollen, painful testis.

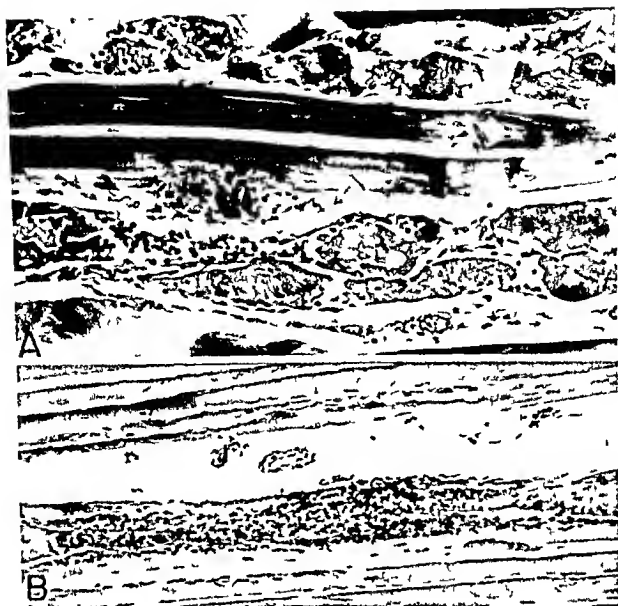


FIG. 17 CHANGES IN SKELETAL MUSCLE

In A (case 6, duration 4 days) there is severe necrosis of muscle fibers, with increase in number of sarcolemmal and interstitial cells. Bodian activated silver method $\times 160$ (AIP Neg. 89522). In B (case 11, duration 15 days) an area of severe focal necrosis with cellular proliferation is to be noted. Remaining muscle fibers are in the realm of normal except for slight hyperplasia of some of the sarcolemmal cells. Hematoxylin and eosin stain $\times 115$ (AIP Neg. 98914).

VII DISCUSSION

In this review of the literature, considerable effort was made to determine the clinical scope of the disorder under discussion. A conclusion reached was that the pathoanatomic terms thus far employed are inadequate. Such a term as "polyradiculoneuritis", for example, although justified in most cases from a clinical standpoint, does not stand up pathologically, for in none of our 50 cases were inflammatory cells observed in the peripheral nervous system until the course was well advanced, and then they were regarded as part of the reparative process. To classify the disorder as a "polyradiculoneuropathy" would be more in keeping with what is seen under the microscope and would be in line with the now widely accepted term "encephalopathy" to denote various noninflammatory disorders of the brain, but such a term is too nonspecific to serve a useful purpose in designating the disorder under discussion.

Some of those who have regarded Landry's paralysis and the Guillain-Barré

syndrome as entirely different disorders have claimed that in Landry's paralysis there are no discernible pathologic changes, whereas in cases corresponding clinically to the Guillain-Barré syndrome the proximal portion of the peripheral nervous system suffers degenerative and other changes. In our cases the pathologic changes varied with the duration of the disorder. Edema of the more proximal part of the peripheral nervous system constituted the only significant alteration during the first three or four days of illness. By the fourth day, slight swelling and irregularity of myelin sheaths were detected, and by the fifth, clear-cut disintegration of myelin and swelling of axis cylinders. On the ninth day a few lymphocytes sometimes began to appear, on the eleventh, phagocytes, and on the thirteenth, a proliferation of Schwann cells. Severe degenerative changes were found in the anterior horn cells in a few cases but they were always less severe than the changes in the roots, and consequently were regarded as retrograde in nature. Even in cases of paralysis unaccompanied by sensory disturbances—cases which most closely simulated Landry's paralysis—the degenerative changes were more advanced in the roots than in the anterior horn cells. Hence, our material lends no support to the view that the anterior horn cells are primarily attacked in Landry's paralysis. In all the cases in which appropriate material was available, the degenerative changes, decidedly focal in early stages of the disorder, were concentrated in the region of the spinal nerves and extended both proximally and distally for a short distance, but whether or not the peripheral nerves also bore the brunt of the attack could not be determined because of the paucity of peripheral nerve material. Where motor symptoms were most prominent the lesions tended to predominate in the anterior roots, and where widespread anesthesia accompanied the paralysis the lesions were found in posterior and anterior roots; this, as far as we could determine, was the only essential pathologic difference between the two clinical forms of the disorder, the lesions were alike but differed in position.

The severity of sensory symptoms has been said by some to be a distinguishing feature between Landry's paralysis and the Guillain-Barré syndrome, mild symptoms characterizing the former and moderate to severe the latter. It is difficult, however, to determine where to draw a line between mild and moderate. If aching, numbness and/or paresthesias, and hypesthesia, alone or in combination, are to be regarded as constituting mild sensory symptoms, there were 13 of our group which fall into this category (table 7). By way of contrast, there were 19 in which there were pain, tenderness of nerves and/or muscles, hyperesthesia, anesthesia, and a reduction in deep sensibility in various combinations (table 8). Comparing the two groups, one finds that the incidence and severity of sensory symptoms tend to increase in direct relation to the duration of the disorder. Widespread anesthesia and hyperesthesia were not encountered until after the twentieth day of illness, except in case 30 in which extensive anesthesia was present on the fifth day. Had the 6 patients who survived 5 days or less (table 7) lived longer, it seems likely from what one observes in other cases, that more severe sensory disturbances would have developed. On the other hand, no difference in sequence of paralysis could be found in the two groups.

There was little correlation in the degree of sensory disturbances and the incidence of increase in spinal fluid protein in those cases in which figures are available, the protein was elevated in 71 per cent in which sensory disturbances were mild, and in 85 per cent in which they were severe.

It has also been claimed that in Landry's paralysis the spinal fluid suffers no change, whereas in the Guillain-Barré syndrome there is pronounced albuminocytologic dissociation. In our series, in which the protein content of the spinal fluid had been determined in 33, and in which the Pandy reaction was positive in an additional 5 cases, making a total of 38, there were 11 in which the protein was within the limits of normal. This constitutes 20 per cent of the cases, and is not an

TABLE 7

Data on thirteen fatal cases of Landry Guillain Barré syndrome in which sensory disturbances were minimal

(+ signifies positive, 0, negative, and —, information not available)

CASE NO	DURATION	NATURE OF SENSORY DISTURBANCES				SPINAL FLUID FINDINGS		
		Aching	Numbness and/or paresthesias	Hyperesthesia	Tenderness of N's and/or M's	Protein	Pandy reaction	Cells
	days					mg. per 100 ml		mm ³
1	2	+	—	—	—	74	—	110
3	3	—	+	0	—	—	—	—
4	3	—	—	+	—	81	—	36
8	4	0	0	0	0	—	—	3
9	5	—	—	+	—	100	+	2
14	5	—	—	—	—	—	—	—
21	6	—	+	0	—	—	—	2
22	6	—	—	—	—	27	—	2
24	8	+	—	—	—	250	+	8
25	8	—	—	—	—	—	—	7
31	10	+	—	—	—	30	—	0
44	22	+	+	+	—	45	0	0
46	23	—	+	+	—	—	+	16

unduly high incidence when a comparison is made with other series, for instance that of Baker (10) in which the spinal fluid protein was normal in 21.5 per cent of 28 cases. It should be emphasized that a single sampling of total protein does not necessarily reflect the level of protein during the entire course, for it has been shown that protein may rise from normal to excessive levels during the course of the disorder, or may be initially elevated and subsequently fall to normal. The former was true in 4 of our cases, and the latter in 1. But granting that the total spinal fluid protein was consistently normal in all 11, the overall clinical picture of these cases differed in no essential from that of the others. As may be seen in table 9, which gives data prior to spinal fluid study, the lower limbs were paralytic in all cases save 2, and subjective or objective sensory changes, or both, were present in all except 1. Duration of the illness was also not a factor in the

non-appearance of an excess protein in the spinal fluid From these data it is apparent that the amount of spinal fluid protein is not of much importance in establishing the diagnosis of the Landry-Guillain-Barré syndrome

The ultimate prognosis in our cases was obviously not influenced by the rise or fall of the spinal fluid protein. where more than one protein determination was made, there was a rise of protein in 6 instances and a fall in 4

TABLE 8

Data on nineteen fatal cases of Landry-Guillain-Barré syndrome in which sensory disturbances were severe

(+ signifies positive, 0, negative, and —, information not available)

CASE NO.	DURATION	NATURE OF SENSORY DISTURBANCES							SPINAL FLUID FINDINGS (N = NORMAL)		
		Numbness and/or paresthesias	Pain	Tenderness of N's and/or M's	Hypertesthesia	Anesthesia	Widespread hyper- and/or anesthesia	Reduced deep sensitivity	Protein	Pandy reaction	Cells
	days								mg per 100 ml		mm ³
16	6	+	+	+	—	+	—	—	—	—	0
17	6	—	+	+	+	—	—	0	—	—	—
18	6	+	+	+	+	—	—	—	76	—	4
20	6	+	+	+	—	—	—	+	34	+	5
23	8	+	+	+	+	—	—	—	135	+	0
26	9	+	+	—	—	—	—	+	100	—	2
27	9	+	+	—	—	—	—	—	—	+	9
28	10	—	+	—	—	—	—	+	114	+	5
30	10	+	+	—	—	+	+	+	18	0	2
33	11	+	+	+	+	—	—	+	155	+	0
37	13	+	+	—	—	+	—	+	—	—	—
38	13	—	+	+	—	—	—	—	50	0	8
40	14	+	+	+	—	—	—	+	106	+	4
42	20	+	+	0	—	—	—	+	—	0	1
43	21	+	+	+	+	+	+	+	75	+	14
45	23	—	+	—	—	+	+	—	—	0	N
48	33	+	+	+	—	+	+	+	333	+	4
49	45	+	+	—	—	—	—	+	375	+	—
50	46	+	+	+	—	+	+	+	59	+	0

The development of the Landry-Guillain-Barré syndrome during the course of infectious mononucleosis in cases 4 and 5 is probably not fortuitous This association has been described by others (101, 156, 167) and has occurred in at least 1 unreported case (46) The etiologic agent of infectious mononucleosis is notoriously neurotropic, as frequently evidenced by symptoms referable to the central nervous system and by the demonstration of changes characteristic of infectious mononucleosis in fatal cases of meningo-encephalitis (70, 119, 202). Our series also included 6 cases in which the histologic changes in the spleen were similar to those of infectious mononucleosis, although no further support for the

diagnosis could be obtained from the available data. It must be remembered, however, that the tissue changes in this disease may be relatively evanescent and the heterophile antibody curves and blood pictures inconstant. While it is likely that infectious mononucleosis is at least one cause of the Landry-Guillain-Barré syndrome, much more careful study of the blood is required in future cases to determine the frequency of this relationship. It is recommended that the blood picture be closely observed throughout the course of the disorder, and that serial heterophile antibody titrations be performed, using the Davidsohn technic, rather than being content with one negative test. Despite the negative results of virus studies in our series it is also urged that attempts at virus isolation be continued.

TABLE 9

Analysis of eleven fatal cases of Landry Guillain Barré syndrome in which spinal fluid protein was within the limits of normal

(+ signifies positive, 0, negative, and —, information not available)

CASE NO	DURATION	INITIAL UPPER RESP INFECT	TOTAL SPINAL FLUID PROTEIN (N = NORMAL)	TOTAL CELLS	SITES OF PARALYSIS PRIOR TO SPINAL FLUID STUDY				SENSORY MANIFESTATIONS PRIOR TO SPINAL FLUID STUDY		
					Lower limbs	Upper limbs	Cranial N's	Inter costals	Pain or aches	Numbness or paresis/esthesias	Objective sensory changes
	days		mg per 100 ml	mm ³							
6	4	+	N	1	+	+	0	+	+	—	—
12	5	—	30	2	+	+	—	0	+	—	—
13	5	+	42	1	+	—	+	—	—	+	+
15	5	—	N	9	—	—	+	—	—	—	+
20	6	+	34	5	+	+	+	+	+	+	+
22	6	+	27	2	—	—	+	+	—	—	—
29	10	+	42	0	+	+	+	—	+	+	—
30	10	+	18	2	+	0	—	—	+	+	+
31	10	—	30	0	+	+	+	—	+	0	0
44	22	—	45	0	+	+	+	—	+	+	+
47	29	—	33	0	+	+	—	—	+	—	—

The problem of classification has engaged the attention of several workers in the field. Guillain (93, 94), all of whose cases were nonfatal, employed a classification based on the topography of involvement, as follows:

1. Involvement of limbs solely
2. Involvement of structures supplied by cranial nerves solely
3. A combination of 1 and 2
4. Instances in which cerebral symptoms are severe

Baker (10), whose cases carried a mortality of 9.1 per cent, proposed a classification in which the degree of severity is also taken into account:

1. *Abortive or mononeuritic form*, occurring in the realm of either the spinal or cranial nerves, or both, relatively benign
2. *Polynuritic form*, also both spinal and cranial in distribution, also generally benign but running a longer course than in 1

3 *Myelitic form*, also of spinal and cranial nerve distribution, with emphasis on the former, the form most frequently encountered, recovery rapid.

4. *Bulbar form*, also of spinal and cranial nerve distribution with emphasis on the bulbar symptoms, death may occur

TABLE 10

Classification of fifty fatal cases of Landry-Guillain-Barré syndrome

TYPES OF CLINICAL COURSE	TOTALS
1 Rapidly developing widespread paralysis, spinal and cranial, in which the sequence of spread is undetermined (sensory disturbances mild to severe) (Cases 1, 2, 3, 4, 9, 12 and 16)	7
2 Paralysis affecting the lower and/or upper limbs first, then cranial nerves and usually intercostals (sensory disturbances mild to severe)	
a with cutaneous disturbances of radicular distribution (Cases 7, 19, 43 and 48)	4
b without cutaneous disturbances of radicular distribution (Cases 5, 6, 10, 11, 13, 14, 17, 18, 20, 21, 23, 24, 25, 29, 31, 32, 33, 34, 36, 37, 38, 39, 40, 42 and 44)	26
3 Paralysis commencing in the limbs and involving the intercostals without implicating the cranial nerves	
a sensory disturbances absent (Case 8)	1
b sensory disturbances present (Cases 28 and 47)	2
4 Paralysis starting in the bladder and spreading to limbs, trunk, and cranial nerves (with cutaneous disturbances of radicular distribution) (Case 45)	1
5 Paralysis starting in the lower limbs, ascending and affecting cranial nerves (sensory disturbances mild to severe)	
a with cutaneous disturbances of radicular distribution (Case 30)	1
b without cutaneous disturbances of radicular distribution (Case 35)	1
6 Paralysis starting in the domain of the cranial nerves and subsequently involving limbs (sensory disturbances mild to severe)	
a with cutaneous disturbances of radicular distribution (Case 50)	1
b without cutaneous disturbances of radicular distribution (Cases 26, 27, 46 and 49)	4
7 Paralysis starting in the domain of cranial nerves and taking a descending course (Cases 15 and 22)	2

5 *Cerebral form*, of rare occurrence, with severe headache, malaise, vertigo, nausea, papilledema, and relatively mild involvement of cranial and spinal nerves, prognosis guarded

Alajouanine and Mauric (4) viewed their cases, occasionally fatal, in another light, as follows:

1 *Les formes algiques*, with subjective and objective changes in superficial and sometimes deep sensibility, variable in distribution and usually radicular, with slight meningeal reaction (5 to 20 cells per c mm of spinal fluid) and 400 to 600 mg per cent of protein

2 *Les formes polynévritiques*, with both motor and sensory disorders, the

former predominating, and abolition of reflexes, with slight meningeal reaction but with 2000 to 3000 mg per cent of protein. This is the form described by Guillain and Barré, recovery generally rapid.

3 *A diffuse form*, involving cranial nerves and sphincters as well as limbs, with motor disturbances predominating over sensory ones, and facial and extraocular palsies being the most frequent of the cranial nerve palsies, often with albuminocytologic dissociation ultimately. This is the form described by Holmes and by Bériet, recovery usually rapid but sometimes slow and incomplete.

4 *A diffuse form with concomitant disturbances of the central nervous system*, characterized by diffuse motor disturbances, discrete alterations in superficial sensibility, dissociation of reflexes (some being absent and others hyperactive), frequent astereognosis, sphincter disturbances, and paradoxical findings in the motor realm (muscular atrophy and contractures of the extrapyramidal type), with albuminocytologic dissociation.

5 *A meningeal form*, of varying intensity, with a diverse accessory motor and sensory symptomatology, sometimes difficult to distinguish from tuberculous meningitis and poliomyelitis.

Our cases differ from those of other series in that they were all fatal. The differences in clinical syndrome consisted not in the neural site of primary attack—for it could generally be demonstrated pathologically that the more proximal part of the spinal and/or cranial nervous system was the site of predilection—but in the levels of the peripheral nervous system first affected, in the sequence and rapidity of subsequent spread to other lower motor neurons, and in the degree of involvement of the spinal cord and brain stem. Taking these factors into consideration, our cases fall into the groups listed in table 10. It will be noted that paralysis is the pivotal point of the classification, the disorder falling into groups predicated on site of origin and subsequent spread, and being qualified by the nature of the sensory disturbances. In this classification, fever, mental disorders, symptoms of meningeal involvement, and the quantity of spinal fluid protein and cells are disregarded because it is believed that they are variables which are coincident to the fundamental disorder in the more proximal parts of the spinal and cranial nerves. Involvement of the neuraxis is included in the classification, but whether widespread paralysis and radicular sensory disturbances can be taken as evidence of both radicular and neuronal involvement could not be decided. Pathologically, the anterior horn cells did not generally suffer to any appreciable degree and except in one instance, no changes were detected in any of the pathways of the spinal cord, although admittedly the lack of demonstrable damage does not necessarily mean that the central nervous system was not affected.

VIII SUMMARY AND CONCLUSIONS

A clinical study of 50 fatal cases of a disorder referred to as Guillain-Barré syndrome, acute infective polyneuritis, Landry's paralysis, and otherwise, confirmed the impression gained from a review of the literature that all fall into a single category. Virtually all the different forms of the disorder which have

been recognized by others are represented in our group. Since pathoanatomic terms are inadequate appellations for the disorder, it was felt that an eponymic designation was necessary. Accordingly, the names of those most indelibly connected with the disorder were selected to cover the group as a whole, and the term Landry-Guillain-Barré syndrome chosen. Such a designation serves to emphasize the potentially serious nature of the disorder. Taken as a whole, the disorder is characterized by a polyradiculoneuropathy which may begin in any peripheral neurons, spinal or cranial, circumscribed or widespread, may affect predominantly the motor or the sensory neurons or both to the same degree, it may remain essentially a radicular disorder or, according to some authors, it may extend into the central nervous system at any point, and either ascend or descend, the outcome usually being dependent on the degree of involvement of respiratory or cardiac nerves. Changes in the amount of protein and the number of cells in the spinal fluid are regarded as incidental to the disorder.

In our series of 50 fatal cases, in which duration varied from 2 to 46 days, the clinical groups recognized are indicated in table 10. Systemic or local infections ushered in the disorder in 40. A latent period between the occurrence of prodromal symptoms and neural attack was observed in 9 of the series. In only 3 instances was there a definitely febrile course. In most of the cases the disorder involved the limbs before it became generalized in the domain of the cranial nerves, trunk and intercostals. Only in 3 did death occur before cranial nerves were implicated. In 4, the disorder commenced exclusively in the domain of the cranial nerves. The nerves of abdominal and/or pelvic viscera bore the brunt of the initial attack in 3. Ascending paralysis, starting in the lower limbs and affecting segment after segment in its climb upward, was noted in 2, and descending paralysis, starting in the cranial nerves, in 2; one gains the impression that this number would have been greater if the patients had been more carefully observed. Widespread radicular distribution of anesthesia or hyperalgesia was observed in 7. It is worthy of note that the incidence and severity of sensory symptoms tended to increase in accordance with the duration of the disorder. Respiratory failure, which could usually be traced to intercostal paralysis, was the final event in the great majority, and in 3 circulatory failure was regarded as the cause of death. Bronchopneumonia and pulmonary edema seemed to be the critical factors in some cases.

Cranial nerves were affected in all cases save 3. Dysphagia developed in 43 and dysarthria and/or aphonia in 33. Palsies of cranial nerves other than the IXth and Xth occurred in the following order of frequency: VIIth in 25 cases, Vth in 14, IIIrd, IVth and/or VIth in 12, and the XIIth in 10.

Spinal fluid studies included total protein determination in 33, and the Pandy reaction in an additional 5, making a total of 38. Protein was increased in 27, or 79 per cent of the 38 cases, the amount varying from 50.5 to 375 mg per cent, and exceeding 150 mg per cent in only 6. A single sampling of total protein does not necessarily reflect the level of protein during the entire course, for in 4 of our series it was observed that protein rose from normal to excessive levels during the course of the disorder, and in 1 was initially elevated and subsequently

fell to normal The over-all clinical picture and the duration of the disorder in cases with normal spinal fluid protein differed in no essential from those in which it was elevated The cell content of the spinal fluid was determined in 44 of the cases and varied from 0 to 110 cells per c mm Only in 5 cases were 20 cells per c mm exceeded Signs of meningeal irritation were observed in 6 cases, in 1 the spinal fluid cell count was normal and in the other 5 ranged from 7 to 25 per c mm In the 2 cases in which the cell count was highest, namely 30 and 55 per c mm, no evidence of meningeal irritation was noted Colloidal gold studies in 22 revealed 10 in the normal range, 4 mid-zonal, and 8 of the first-zone type

Total and differential leukocyte counts of the blood were available in 22 cases, excluding the 2 associated with infectious mononucleosis In 12 of these there was a relative and absolute increase in lymphocytes early in the course of the disorder, the total number varying from 3,900 to 8,281 and the percentage values from 25 to 80 A tendency to lymphocytosis has, to our knowledge, not been previously reported as a feature of the Landry-Guillain-Barré syndrome

It is of exceeding interest that malignant hypertension developed during the course of the illness in one fifth of the cases, an observation which should lead to a reinvestigation of the role of the spinal roots and cranial nerves in the development of hypertension

Study of the central nervous system revealed nothing of consequence in the spinal cord, brain stem, or cerebrium, aside from mild to moderate and occasionally severe changes in anterior horns of the spinal cord and motor nuclei of the brain stem, which were regarded as retrograde Occasional scanty collections of perivascular lymphocytes were noted in the central nervous system in approximately one fourth of the cases, and a slight reaction in the leptomeninges in about one-third, both were relatively inconsequential There was little pathologic evidence to support the clinical impression that the morbid process sometimes extends into the neuraxis

The peripheral nervous system, on the other hand, was consistently affected, the lesions being concentrated in the spinal nerves, i e, in the region where the anterior and posterior roots fuse, and extending for a short distance proximally and distally There was insufficient material to determine the relative degree of involvement of the peripheral nerves The study afforded the opportunity of determining the approximate sequence of the changes, edema during the first 3 or 4 days, beginning swelling and irregularity of myelin sheaths and axis cylinders on the fifth, appearance of a few lymphocytes on the ninth and phagocytes on the eleventh, and Schwann cell proliferation on the thirteenth The changes in myelin, axis cylinders, and Schwann sheaths were progressive, so that by the forty-sixth day, the maximum duration in our group, some of the spinal roots and peripheral nerves were devastated Lymphocytes, which tended in some cases to increase in number as time went on, were regarded as a part of the reparative process As to correlation of the location of the pathologic findings with the clinical picture, it could generally be demonstrated that the anterior roots were solely or predominantly affected when paralysis was unaccompanied by severe sensory disturbances, and that both anterior and posterior roots bore

the brunt of the attack when paralysis was associated with anesthesia, the lesions were of the same kind in these two conditions, but differed in location

The most striking change elsewhere was in the lungs, where bronchopneumonia, usually in an early stage, was encountered in 33 cases. In no instance was frank interstitial pneumonitis ("virus pneumonia") observed. Other changes included mild focal myocarditis in 7, mild focal necrosis of the liver in 2, focal necrosis of the adrenal cortex in 1, lower nephron nephrosis in 3 and changes suggestive of this condition in an additional 5, degenerative and/or inflammatory changes of varying intensity in skeletal muscle in 4, and changes suggestive of infectious mononucleosis in the spleen in 6 and in the lymph nodes in 1.

No conclusive evidence regarding the etiology of the disorder is presented, although the association of infectious mononucleosis has been proved in 2 cases and suggested in 6 of our series. Virus studies carried out in 17 instances were negative, and bacteriologic studies in 13 cases yielded such a diversity of organisms that no one could be incriminated.

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ERRATUM

The title page preceding the contents of volume 27 in the December 1948 issue erroneously listed the old Editorial Board. Corrected page is reprinted opposite

ERRATUM

In the February 1949 issue of *MEDICINE*, Volume 28, Number 1, in the article entitled The Pathology of the Thymus in Myasthenia Gravis by Benjamin Castleman and Edgar H. Norris, three figures were inadvertently transposed. Corrected, they would appear as follows:

The photograph printed as figure 21 is the photograph for figure 23

The photograph printed as figure 22 is the photograph for figure 21

The photograph printed as figure 23 is the photograph for figure 22

THE ETIOLOGY OF RHEUMATIC FEVER. A REVIEW OF THEORIES AND EVIDENCE

Byron H. Waksman, M.D.*

INTRODUCTION

Rheumatic fever, as the first cause of death between the ages of 5 and 19 years (291, 668, 678), and the cause of approximately 35 per cent of all heart disease (668, 678), is a vital subject for research (Details on incidence and mortality are found in references 21, 237, 268, 283, 458, 460, 461, 534, 663, 668, 669, 707). At present it can only be classified as a member of a little understood group of diseases which includes rheumatoid arthritis, glomerulonephritis, lupus erythematosus, periarteritis nodosa, thromboangitis obliterans, dermatomyositis, scleroderma and perhaps others. These have often been grouped together (38, 45, 138, 171, 203, 340, 341, 342, 348, 369, 503, 504, 531, 538, 557) because of known instances of overlapping and because of clinical and pathologic similarities.

The period in which the etiology of rheumatic fever has been the subject of hypotheses which could be tested against facts has lasted about sixty years. Prior to this, knowledge of rheumatic fever increased only in the clinical and pathologic-anatomic spheres (for historical reviews, consult references 184, 437). In the years between Sydenham's description of rheumatic fever and chorea in 1666 and the first microbial hypothesis in 1883, no particularly coherent etiologic hypothesis existed aside from a vague notion that all the rheumatisms were due to a diseased condition of the nervous system, a concept revived recently by Spersky (587).

Many reviews have been written about rheumatic fever. As most of these deal, however, with work carried on in circumscribed areas of the field or over limited periods, there appears to be some need for a review tracing the main currents of thought concerning the etiology of this disease. The present review is an attempt to fill this need.

THE FACTOR OF INFECTION

Before 1900, many different organisms were cultured from the blood, joint and pericardial exudates, heart valves, periarticular tissue and subcutaneous nodules of patients who had rheumatic fever. Some workers found streptococci or diplococci (396, 633, 634), others identified gram-positive spore bearing bacilli (51, 396, 624), and still others incriminated staphylococci (579). Since the work of Poynton and Paine (485, 486), however, the streptococci have with few exceptions (122, 178) held the center of the stage. The first papers did not specify the types of streptococci isolated (284, 485), but most earlier workers found green-producing (90) or indifferent streptococci (40, 41, 582) or both (528, 701). Rosenow claimed (528, 529, 530) to be able to distinguish culturally streptococci affecting

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the joints from those affecting the heart. More recently, Cecil and his co-workers (79) found, in more than half of the patients studied, blood cultures of what they at first thought to be an alpha streptococcus and later decided was an attenuated beta streptococcus, their so-called typical strain.

These findings did not go unopposed. In 1903, Philipp (478) found negative blood cultures in 31 rheumatic patients. Swift and Kinsella (615) showed that the green-producing streptococci that they isolated from the blood or heart valves of 10 per cent of their patients had no constant cultural or serologic characteristics. Dawson, Olmstead and Boots (136) using Cecil's method found alpha streptococci in sterile agar tubes more than half the time. Nye and Waxelbaum (451), who were unable to confirm Cecil's findings, quoted evidence (379, 454) showing that contamination with green streptococci occurs as readily as with staphylococci or diphtheroids. Lichtman and Gross (367), after similar failure to confirm Cecil, surveyed the fallacies inherent in the study of cultures from material taken from patients with rheumatic fever. They quoted Epstein and Kugel (173), who found streptococci in 40 per cent of normal valves, Shands (571), who found them in 2 of 10 Charcot joints and in 1 joint affected with gonorrheal arthritis, and Menkin (414), who showed that organisms localize secondarily at any inflamed site. An extensive survey, made by Callow (70) on the nature of the organisms in blood cultures from different diseases, showed definitely that cultures from patients who had rheumatic fever were not different from those taken from other patients who had respiratory diseases. This has been confirmed by Leslie and Spence (364). Cecil has modified his statements (15), and it is now accepted, provisionally, that characteristic bacteria cannot be isolated from the blood stream, heart or joint tissues of rheumatic patients.

Efforts to demonstrate a virus appeared successful when Schlesinger and his co-workers (547) obtained by centrifugation of pericardial and pleural exudates of dead rheumatic patients suspensions of particles, which much resembled other viruses and were agglutinated only by serums of rheumatic patients. However, although these findings were confirmed (119, 156), the disease could not be reproduced by injection of a suspension into animals (155, 157) or by injection of any materials from patients who had rheumatic fever (15, 244, 430, 604, 678). Efforts by Angevine and co-workers (15) to find pleuropneumonia type organisms by culturing a variety of rheumatic materials on special mediums, chorio-allantoic membranes of chicks and so forth, failed. Swift and Brown (607), who believed that they had found such organisms in serial transfers in mice, later discovered that their organism was a natural pathogen of the mouse. More recently, MacNeal and his associates (388, 389, 390), by injecting intravenously blood, pericardial exudates and other material from severely ill patients into rabbits, produced gross and microscopic lesions closely resembling those of rheumatic fever. They were able to pass the supposed infective agent in bacteria-free form through fifteen generations of rabbits and also to inoculate the chorio-allantoic membrane in hen eggs, from which the agent was recovered in intensified (concentrated?) form. MacNeal gives credit for earlier work of

this type to Andrei and Ravenna (12) They, however, produced experimental lesions not only by using materials from rheumatic patients but also by inducing focal infections in animals with a variety of streptococci, an unrelated technic, and were careful to state that the lesions were not identical with those of rheumatic fever (499) Copeman (127) injected blood from a rheumatic patient into human volunteers in whom rheumatic symptoms, fever and an increased sedimentation rate subsequently developed Confirmation of his observations would be desirable

Associated with the effort to demonstrate pathogenic organisms in the body has been the effort to show that rheumatic fever behaves as an epidemic disease or is associated with epidemics of pharyngitis or tonsillitis In 1886, Haig-Brown (256) found that when tonsillitis developed in 345 previously healthy boys, heart disease subsequently appeared in 29 of them Hirsch (287) considered rheumatic fever infectious Newsholme, with his great mass of statistics, showed that its behaviour, seasonal, geographic and otherwise, was that of an epidemic disease A number of studies appeared during and after World War I (218, 219, 236, 358, 502), reporting epidemics of rheumatic fever with evidence of bed-to-bed infection (236) and pointing out the parallelism of rheumatic fever and infectious diseases such as tonsillitis and cerebrospinal meningitis at crowded military depots (218) Since 1930 and particularly during World War II, confirmatory evidence has appeared (48, 230, 231, 232, 237, 337, 466, 639, 671) Epidemics of pharyngitis or tonsillitis in known rheumatic patients, followed by recrudescences of rheumatic fever, have been studied in detail (121, 220, 545, 576) A paper by Madsen and Kalbak (392) described the marked rise in incidence of rheumatic fever following two epidemics of streptococcal angina spread by milk Wilson, on the other hand, was (678) and is (681) opposed to the idea that rheumatic fever is infectious She analyzed data on the occurrence of rheumatic fever in different members of the same families to test the hypothesis that the disease is infectious, using methods of Chapin, Frost, Opie and others, and found no evidence that it is She pointed out that in any family the age of onset, generally agreed to be between 5 and 10 years (140, 320, 462, 573), is the same for secondary infections as for primary, in contrast to known infectious diseases such as measles

The impetus to investigations since 1930 has been supplied by the studies of Coburn (95), who correlated the incidence of rheumatic fever with that of hemolytic streptococcal infections and insisted that every attack of rheumatic fever must be preceded by such an infection, with an interval of two or three weeks He stressed the fact that rheumatic fever is rare in the tropics as are hemolytic streptococcal infections, is commonest in the poorer classes and has its greatest incidence in the winter and spring

To take up these points individually Coburn's original contention regarding rheumatic fever in the tropics has had to be modified considerably Those who agreed with his thesis quoted the work of Clarke (89), who showed from government statistics, his own experience and quoted work of others that in the true tropics rheumatic fever does not exist This conclusion has been amply con-

tradicted by the finding of a number of workers that rheumatic fever is not uncommon in the tropics (25, 125, 197, 261, 267, 359, 413) Coburn and Paul (105) stated that scarlet fever and, by implication, other hemolytic streptococcal infections are rare in the tropics Yet Plummer (484) found that while only 64.6 per cent of a series of Canadian serums contained more than 1 Washington unit of streptococcus antitoxin, 93.5 per cent of a similar series of tropical serums did, the mean potency of the latter being considerably higher This implies a high frequency of hemolytic streptococcus infection in the tropics, a conclusion that Plummer also supported with the results of extensive Dick testing Nevertheless, rheumatic fever is less frequent in warm than in cool climates (314, 445, 446, 464) Within the United States a marked difference in incidence exists between states (702) The highest incidence is found in the mountain and Great Lakes regions (291, 669) (Altitude does not appear to be a factor (662)) These differences are particularly apparent in comparative studies carried on in Army and Navy posts in various parts of the country (290, 502, 639) A study (539) in three California towns showed that the incidence of rheumatic fever was greatest where the year was uniformly cool with high precipitation and lowest in a warm, dry climate Further confirmation of this point has been obtained in studies on rheumatic children, who, after transportation to warm, dry areas like Miami, show a lowered incidence of streptococcal infections and of rheumatic fever, though having the usual number of colds, bronchitis, measles and so forth (521) The reason for the effect of climate remains in doubt The effect of artificial warm climate on rheumatic recurrences has been discussed by Edstrom (167)

Rheumatic fever does have its greatest incidence among poorer people (105, 301, 299, 465) Perry and Roberts (476) found that the rheumatic fever incidence in Bristol school children was associated with the density of children per room The Wedums (660) have made an interesting epidemiologic study in Cincinnati, showing a definite correlation between rheumatic fever incidence and dwellings, crowding, persons per acre and other environmental factors On the other hand, Kaiser (320) and others (682) found the highest incidence in the well-to-do laboring classes Hill (286) noted that rheumatic fever is rare among the Eskimos, who, although subject to a severe "macroclimate", live in a comfortable "microclimate" and therefore resist the disease easily

As to the season of incidence, Coburn and Pauli (105) observed that rheumatic fever parallels respiratory infections with hemolytic streptococci, with its greatest frequency in winter and spring This has been confirmed by a number of reports (83, 98, 320, 411, 573) beginning as far back as those of Hirsch (287) and Newsholme (444) The latter showed that the incidence of rheumatic fever parallels scarlatina, pyemia, puerperal sepsis and erysipelas More recently Atwater (22) has made the same observation It is obvious, however, that a common seasonal incidence does not imply a common etiology (671, 678)

Most of the epidemiologic investigations mentioned in previous paragraphs were carried out with the implicit or explicit assumption that rheumatic fever is associated with upper respiratory streptococcal infections (317, 483) What is

the direct evidence on this point? In 1927, Birkhaug (40, 41) and Small (582) isolated anhemolytic streptococci from the throats and blood of rheumatic patients. Their bacteriologic results indicated that the two organisms were the same. Small found that agglutinins to his organism increased during a rheumatic attack while opsonins decreased. He named it "*Streptococcus cardioarthritidis*" and attempted to immunize patients passively against it in the acute phase. He claimed excellent therapeutic results although he used only 9 patients, of whom 1 later proved to have gonorrheal arthritis and another rheumatoid arthritis. The later papers (583, 584), in which he described the effect of vaccines of this organism, did not present statistical data. Criticism of his conclusions appeared in the *Journal of the American Medical Association* (705, 706), pointing out that identical work had been done before by Menzer (415, 416, 417), who himself had realized (418) that the seemingly beneficial results obtained with immune serums were quite nonspecific, in the nature of irritation or protein therapy. Birkhaug's work was more productive. He isolated a toxin from his organism which, when injected in small quantities intradermally, gave a higher percentage of positive reactions among rheumatic patients than among controls.

Since these papers appeared, other workers (302, 666, 670) have shown that the throat flora of rheumatic patients differs in no way from that of other persons. Andrewes, Derick, and Swift (13) have shown that the hemolytic streptococci found there have no relation to each other culturally or serologically. A possible exception is provided by the finding (378) of a high incidence of "minute" hemolytic streptococci in the throat in cases of acute rheumatic fever.

In contrast to these negative observations, hemolytic streptococci have been isolated from rheumatic patients before attacks by most workers in the field (105, 106, 238, 290, 291, 606). In particular, the studies carried out at various Army posts leave no doubt on this point (98, 290, 639). The success of sulfonamide compounds (24, 28, 97, 102, 103, 147, 181, 290, 356, 357, 581, 625, 626, 693) and penicillin (394) in lowering the incidence of upper respiratory infections and rheumatic recurrences in rheumatic children, and on a much larger scale in the armed services, has demonstrated the importance of the hemolytic streptococcus at least in initiating the rheumatic attack (for dissenting views, see 124, 681). The same significance may be attached to the lowering of rheumatic recurrence rates by vaccination with streptococcus toxin or toxoid (150, 656) and to the questionable beneficial effect of tonsillectomy before an attack (212, 214, 299, 301, 320, 321, 387).

In spite of widespread agreement that streptococcal infection precipitates rheumatic attacks, no one type of streptococcus has been successfully incriminated (639, 659). There are always rheumatic attacks not preceded by clinically or culturally demonstrable infection (46, 51, 164, 214, 320, 627). This may be as high as 37 per cent (313). In an attempt to demonstrate that streptococcal infection must precede *all* rheumatic attacks, Cohurn and Pauli (107, 116) determined the antihodies against hemolytic streptococci and their

various products (see Swift (606) for a review of types of tests and methods of testing) They found variable agglutinins, but showed that precipitin, complement fixation and antistreptolysin-O titers were negative in controls and positive in patients who had streptococcal infections or acute rheumatic episodes They observed (108, 109, 110) that when a rheumatic patient had an infection not followed by a rheumatic exacerbation, the antistreptolysin titer failed to rise, and that in an attack (113), the elevation of titer paralleled the severity of the attack Coburn (96) found that an exacerbation during subsidence of an attack is heralded by a fall of titer followed by a rise to a new peak He pointed out (96) that in only 10 of 2,000 cases were the patients children less than 3 years of age (he mentioned evidence (371, 688) showing that antistreptolysin response is weak in patients less than 3 years of age) and that these showed high titers In short, he appeared to have shown that all attacks or recurrences of rheumatic fever are associated with a rise of the antistreptolysin-O titer of the patient (98)

Other workers failed to confirm this Though the elevated titer was usually observed (67, 495, 623, 629, 691, 692), almost all have reported some rheumatic attacks without it, 15 of 110 attacks in one series (229), 21 per cent in another (440) Wilson and co-workers (687) found none in two-thirds of the attacks not preceded by clinical infection and frequently observed a rise of titer in the absence of hemolytic streptococci She failed to find any correlation between rheumatic attacks and antistreptolysin titers, but the high basal value which she used for antistreptolysin may have masked any changes Lower basal figures have been established by Longcope (381) and by Coburn and Pauli (108, 115), who showed that, though the basal value varied considerably with latitude, it was always less than that chosen by Wilson As regards the remaining antibodies, Coburn's findings have been confirmed Agglutination against beta streptococci was not found by some workers (411, 456, 702), was found in most cases by others (222, 448), and appeared in about half the patients in some series (221, 329) Precipitins were usually increased (435, 546, 614, 702), even in patients who, after a streptococcal infection, had no rheumatic attack (548) Antifibrinolysin was increased (47, 254, 435, 441, 493, 594, 628, 646, 691) to the same degree as in normal persons after streptococcal infection (471) Increased titers of complement fixing antibodies to streptococcal nucleoprotein have been observed (265) In short, in acute rheumatic fever, the agglutinins of the patient against hemolytic streptococci usually are increased, and the precipitins, antifibrinolysins and antistreptolysin-O frequently are Antistreptolysin-S apparently decreases during the acute attack (99, 630)

It is apparent then that not all rheumatic attacks are preceded by a streptococcal infection The fact that sulfonamide compounds and penicillin are ineffectual when administered after the onset of an attack (124, 194, 497, 616, 636, 658) is additional proof that the initiating infection is not the direct "cause" of the disease but acts only by starting in motion some more complex mechanism This was succinctly put by Hench and collaborators (278) in 1938: "The majority now consider the prodromal respiratory infections to be non-specific provoca-

tives." Other types of infections may act as the initiator. Copeman (126), studying a small group of British troops in the desert, noted that of 43 attacks of acute rheumatic fever, 8 were preceded by malaria, 7 by dysentery, 6 by sand-fly fever and only 4 by streptococcal infection. Trauma has frequently been noted as the exciting cause of an attack (46, 216, 313, 527). Cold, dampness or excessive fatigue were incriminated in a number of Copeman's cases. Even psychic trauma has been mentioned (78, 527) as a possible precipitating factor. Coburn and Pauli (114) reported a series of splenectomies in rheumatic children, almost all followed by recrudescences of the disease. Attacks may be initiated by tonsillectomy (527), immunization with bacterial proteins or horse serum, sunburn, fracture or tooth extraction (98).

Trauma itself plays a complex role, since it appears to some extent to determine the localization of the pathologic changes which may appear. Swift (605) and Swift and Cohn (608) observed that rheumatic polyarthritis, which frequently involves the knees and ankles first, appears in needle workers and laundresses in the hands and arms first. They remarked that the endocardial lesions appear actually at a highly traumatized location, the valvular line of closure. Edstrom (165) has demonstrated for the closely related disease, rheumatoid arthritis, that occupation, accidental trauma, even left-handedness may be reflected in the clinical picture. Typical rheumatic subcutaneous nodules have been produced by Massell, Mote and Jones (397, 434) and others (266) by injecting blood or saline solution subcutaneously over the olecranon, with or without subsequent friction, in 90 per cent of patients who had active rheumatism, 50 per cent of patients having only laboratory evidence of the disease, 14 per cent of patients whose disease was quiescent and 0 per cent of controls. Mirsky (432) has done the same using subcutaneous injections of trypsin, on the hypothesis that rheumatic fever represents the action on mesenchymal tissues of proteinases, when activated *in vivo* by streptococcal fibrinolysins or after cellular damage resulting from infection, trauma or "anaphylactoid" reactions. According to this hypothesis, a susceptible person is one who does not adequately inhibit these proteinases.

THE FACTOR OF ALLERGY

In 1928, Zinsser and Yu (701) reported the isolation of a variety of streptococci from the myocardium and spleen of rheumatic patients. They suggested that such streptococci act as foci of infection in a hypersensitive host, rheumatic fever would then be an allergic manifestation. They mentioned previous work of Zinsser and Grinnell (700) in which joint changes were produced in sensitive guinea pigs by intra-articular injection of the sensitizing organism. This experimental result was anticipated. Articular and cardiac lesions strongly suggestive of rheumatic fever have been produced by anaphylactic or allergic methods since Cole's work (118) in 1904. Antigens used have included living or dead streptococci (23, 93, 175, 243, 398, 420) and their products (284), tubercle bacilli (11), dysentery organisms (199), foreign serum (60, 61, 204, 210, 221, 315, 343, 380, 403, 420, 429, 640), egg albumin (315, 380, 403, 506, 507, 564),

even the animal's own tissues (305) Much the same results have been obtained by injection of the antigen into the joints of sensitized animals (8, 9, 10, 204, 221, 315, 640, 700), a method popularized by Klinge (347), and by repeated intravenous injection of antigen (50, 118, 196, 284, 315, 403, 429, 506, 507, 520) Intrapericardial (23, 564) and intratonsillar (11) injection have also been used Trauma or cold applied to individual joints were found by Klinge to precipitate arthritis (see discussion of alarm reaction)

In an effort to make more precise the character of the immune response, Swift and his co-workers carried out elaborate studies (14, 142, 144, 288, 609) on rabbits into which various types of streptococci were injected intravenously or intradermally. They suggested (600) that rheumatic fever, by analogy with their results, might represent infection in a hypersensitive host, while bacterial endocarditis represented infection with the same agent in an immune host (patients who have bacterial endocarditis are insensitive to streptococci or their products (297, 338) while rheumatic patients are sensitive)

A revival of interest (6, 7) in this type of experimental technic has been occasioned in the last few years by the work of Rich and Gregory, who injected large doses of horse serum or egg albumin into rabbits either several times or in alternation with sulfadiazine and produced a generalized picture similar to that of periarteritis nodosa, with pulmonary and cardiac lesions resembling those of rheumatic fever and renal lesions suggesting glomerulonephritis (235, 503, 505, 506, 507, 508) Rich (503) has collected clinical evidence to demonstrate the frequent occurrence of periarteritis nodosa in serum sickness and during sulfonamide therapy, and its predilection for persons who have other allergies His experiments have been confirmed by Hopps and Wissler (294), who did not, however, observe the renal lesions Both groups of investigators felt that the ease with which they produced periarteritis nodosa, an uncommon disease clinically, was due to the relatively large doses of allergen administered That this may be true is suggested by the work of Fox and Jones (196) who, using a different injection scheme and smaller doses of allergen, produced cardiac lesions and vascular and perivascular lesions in other organs, all however of very mild degree with no true vascular necrosis Robinson (520) using only a single large injection of horse serum obtained no such lesions, but found his animals more susceptible to carditis, nephritis, arthritis, and encephalitis induced by subsequent injection of streptococcal filtrate

It appears, however, that Aschoff (18) did not consider cardiac lesions produced by these techniques typical for rheumatic myocarditis, and Masugi and co-workers (398, 403) have stated that these lesions correspond rather to those of periarteritis nodosa It will be noted that in unrelated types of experiments, such as Selye's, the production of the picture of periarteritis nodosa is accompanied by the appearance in the heart of lesions presumed to be rheumatic This may be an example of a tissue with a limited number of possible responses Gross and his co-workers (243) and others (519) have suggested that both types of lesions are minor variations of the same response, i.e. of a partially immune host to a pathogen of low virulence

It has been shown (360) that lesions induced by this method may be largely or completely prevented by benadryl or other antihistaminic drugs, though these agents do not affect the Arthus response in passively sensitized animals (187) Salicylates also affect lesions of this type considerably (193, 585, 595) This effect is explained variously as due to inhibition of antigen fixation in the tissues (595) or to decreased antibody formation secondary to the destruction of lymphoid tissue by the alarm-reacting effect of salicylates (193) (colchicine is also effective) Hawn and Janeway (270, 271, cf also 309), using whole bovine serum, pure bovine gamma globulin and crystalline bovine albumin for single intravenous injections, showed that the distribution and time of appearance of the lesions depended on the antigen used The gamma globulin gave lesions largely in the glomeruli and heart, to a lesser extent in the liver and joints, while the albumin gave widespread arterial involvement They believed that the lesions depended on the combination of antibody with residual antigen in the involved tissues Ehrlich, Forman and Seifter (169) have distinguished an immediate effect of the first antigen injection, a delayed reaction associated with the appearance of antibody and resembling rheumatic fever a good deal, and a severe sudden reaction following a second injection and resembling periarthritis nodosa closely They consider these last two as representing a delayed or subacute Arthus and an acute Arthus reaction, respectively

Birkhaug (40, 42) was the first to perform skin tests on rheumatic patients with a suspected allergic antigen He used the toxic filtrate of the anhemolytic streptococcus isolated from similar patients He later (43) made large numbers of tests, using filtrates of all the types of streptococci, and invariably found a high percentage of positive reactors among rheumatic patients to the toxins of alpha and gamma streptococci but not to that of beta streptococci This work has been amply confirmed (111, 302, 319, 611, 678) Swift, Wilson and Todd (617) found a higher percentage of positive reactors among active than among quiescent rheumatic cases Other workers have made similar tests using extracts of streptococci such as the nucleoprotein fraction or the "M" proteins (621, 622) as antigen Although a few have found positive reactions in rheumatic patients to extracts of all three types of streptococci (442, 610) and others have found no effect with any streptococcal extracts (212, 385), the majority have found a positive reaction only to extracts of hemolytic streptococci (123, 222, 227, 320) Similar results are reported using whole streptococci as antigen (213, 654)

The non-specificity apparent in results of this type was emphasized by Short, Dienes and Bauer (577), who tested 102 vaccines, obtained from the throats, stools, teeth and so forth of 34 patients with rheumatoid arthritis, on groups of 4 patients, including the patient from whom the organism was isolated They found no consistent result as to organism, *Escherichia coli* and *Neisseria catarrhalis* frequently gave more marked reactions than streptococci The patient who reacted strongly to his own organisms also reacted strongly to others Schultz (557) and Jones and Mote (312) found that rheumatic patients reacted to plain rabbit serum This would seem to mean that rheumatic patients may

be sensitive to streptococci and their products only as a phase of a general allergic hyperirritability. Wilson and her co-workers (687) noted that rheumatic children average five respiratory infections for every three in normal children. A non-specific hyperirritability, such as that suggested, would, in Urbach's cumbersome terminology, be called "metallergy" or "polyvalent pathergy" (637).

The results obtained with vaccines and antiserums are instructive (64). The work of Menzer and Small on nonhemolytic streptococci has been mentioned. Coburn and Pauli (112) were not successful in their efforts to immunize rheumatic patients actively or passively against hemolytic streptococci. Hench and his colleagues (281) noted that in the entire literature for 1939 there appeared no new work on vaccines or antiserums, an indication that this field had become sterile. Occasional papers are still published on this theme (233, 613, 655, 686). The interesting fact that has come out of such work is that injection of some of the antigens used was followed by an exacerbation of symptoms (583, 584). Swift and co-workers (612) found this phenomenon in their tests with streptococcal vaccines or nucleoproteins and compared the effect to that of an overdose of tuberculin in a tuberculous patient. Bland and Jones (46) produced mild recurrences of rheumatic fever by a single injection of typhoid and paratyphoid vaccine. It has been shown that the effect of repeated bouts of fever induced by typhoid and paratyphoid vaccine in chorea is a well-marked shortening of the attack (30, 72, 597). Furthermore pyrexia has been used (578) in the treatment of rheumatic fever. These results are reminiscent of the effects of fever or foreign protein therapy in certain allergic diseases. They support the idea of a non-specific allergic sensitivity in rheumatic fever.

In many ways, the manifestations of rheumatic fever suggest an allergic process (38, 98, 365, 368, 369, 487). Talalaeff (620) has summarized the points favoring this view: absence of immunity, frequency of recurrence, sudden onset and relation to a precipitating illness. The basic pathologic change in this disease, that is, fibrinoid degeneration of collagen, was considered by Gerlach (210), Klinge (347) and Rossle (531) to be characteristic of allergic-hyperergic inflammation (637), though Klemperer and his group (340, 341), who have agreed to the importance of fibrinoid collagen change, have been unwilling to accept it as characteristic of any type of allergy. In rheumatic families there is found a high incidence of clinical allergy, such as asthma, hay fever and eczema (517, 632). In rheumatoid arthritis, injection of streptococcal protein causes leukopenia, (637), much as the ingestion by allergic patients of food to which they are sensitive causes leukopenia, while other bacterial proteins give leukocytosis. The apparent similarity between rheumatic fever and tuberculosis the prototype of bacterial allergy, will be recalled here (27, 412, 455). Rantz, Boisvert and Spink (494), after a thorough sifting of evidence, have concluded that rheumatic fever is *invariably* induced by infection with hemolytic streptococci and must therefore be a manifestation of a general sensitivity of the tissues to some product necessarily common to all the different types.

One rather circumstantial bit of evidence is put forward to support the view

that rheumatic fever involves some allergic process. Salicylates inhibit the precipitation of antigen by antibody to a greater degree than other similar anions (101), and apparently also inhibit antibody formation (293, 306, 599, 473 *contra*). They are said to decrease the severity of anaphylactic shock (71) though not that of the Arthus phenomenon (187). The relief of some rheumatic conditions by salicylates (98) may result from these facts. The arthritis of serum sickness may be markedly decreased in patients treated with neocinchophen or acetylsalicylic acid immediately after serum therapy, this decrease being associated with a decrease in precipitin antibodies (143). The confusion existing in regard to the role of salicylates is evident from the fact that while salicylates will reduce an elevated sedimentation rate *in vitro* (34, 292, 370), it has also been suggested (498, 651) that the lowering of the sedimentation rate in rheumatic fever is brought about by the decrease in fibrinogen resulting from hepatic damage known to occur during salicylate therapy. In any case, salicylates are not believed at present to affect the evolution of the permanent pathologic changes of rheumatic fever (264, 438, 653, 664, 665).

Objections to the explanation of rheumatic fever as a type of allergy have not been lacking (3, 17). Harris (262) and Sayle (542) have pointed out that the percentage of positive cutaneous reactions is less among rheumatic patients than in other streptococcal diseases and sometimes not significantly different from the percentage among normals, that many streptococcal diseases, such as erysipelas, are never followed by rheumatic fever although the organism is identical with other hemolytic streptococci (330), that skin-positive patients need not have a rheumatic attack after a beta streptococcal infection, and that the interval between the precipitating infection and the rheumatic exacerbation is almost constant instead of decreasing with successive attacks as in other allergies. Freeman (198) has summarized the situation as follows: "We are working in a fog and have as yet no clear vision. The word allergy is, to my mind, not a gleam of sunshine breaking through, but an extra wisp of fog." The hypothesis that rheumatic fever is a non-specific allergy would do away with some objections, but it is apparent that something more is required for an adequate understanding of this disease.

A new hypothesis involving the immune mechanism has recently attracted considerable attention (336). It is suggested that rheumatic patients form antibodies against artificial antigens consisting of denatured proteins of their own tissues or of tissue proteins combined as haptens with some streptococcal or other material. The antibodies are capable of combining with the original undenatured or uncombined tissue protein, and clinical symptoms result whenever their titer is high enough to permit their combining with, and damaging, the tissues in question (98, 518). Such a mechanism would be referred to as "auto-endogenous allergy" in Urbach's classification (637). This hypothesis was first developed for glomerulonephritis, which resembles rheumatic fever in that it follows infections with streptococci and shows exacerbations. The two diseases are frequently found together (45, 171, 310, 538), and patients who have glomerulonephritis give a positive cutaneous reaction to streptococcal filtrates

(259) as well as to rabbit serum (non-specific sensitivity) (557). The antistreptolysin-O pursues a course in an exacerbation of nephritis similar to that in a rheumatic attack (158, 159) (for further discussion of similarities and differences, see 563, 565). Masugi was able to produce glomerulonephritis in experimental animals by the intravenous injection of serums containing antibodies against the animals' own kidneys, so-called nephrotoxic serums (this was done by earlier workers (677), without detailed pathologic analysis). He and his associates proceeded to perform a similar experiment with cardiotoxic serums—that is, serums containing antibodies against heart muscle (402) but did not use enough material to yield a conclusive result. Yet he stated that the lesions produced resembled those described by Klinge (344) as characteristic of rheumatic fever. It is interesting that cardiotoxic serums were studied as early as 1902 (81, 182, 183, 536).

Cavelti has recently produced auto-antibodies (76, 77) in rabbits and rats, using as immunizing antigens mixtures of their own heart muscle, skeletal muscle and connective tissue with streptococci or their products. The cardiac lesions appearing in those rats in which antibodies against rat heart or rat connective tissue developed were unfortunately not typical of rheumatic fever. Similar inconclusive results are reported by Bauer (31). Schultz and Rose (558), by incubating hemolytic streptococci with various materials, obtained what they called "albumin-bacterioplasm conjugates", possibly acting as artificial antigens. These reproduced the picture of rheumatic fever in experimental animals and gave severe cutaneous reactions, even flare-ups, in rheumatic patients. Serums of convalescent patients decreased this toxicity. It may be noted that these findings were not well controlled, one would expect the streptococci alone or such of their products as might be expected to appear in these "conjugates" to produce similar results.

Coburn became an adherent of the auto-antibody hypothesis in 1939. He and Pauli (117) demonstrated that a foreign substance appeared in the blood in phase II (phase I is the precipitating infection, phase II the afebrile period, and, phase III the rheumatic attack), that a precipitin against it appeared in phase III, and that this precipitin appeared in all rheumatic patients during an attack. They showed that, in rheumatic patients who were infected but did not suffer from an attack, the antigen in phase II was present but no antibody appeared, whereas in normal persons neither was present. The precipitin was not absorbed by killed hemolytic streptococci of the strain infecting the patient and did not sensitize guinea pigs to anaphylaxis with these streptococci (99). Cross precipitation was possible between all his patients, but he had a small series and has not reported further observations of this type. The Wedums (661), in an attempt to disprove his findings, studied a number of patients with various illnesses including rheumatic fever, and showed that precipitins of the same type could be found in several diseases but less frequently than in rheumatic patients. This fact may have a definite relation to the observation of Hall and Anderson (257, 258) that rheumatic lesions can be found in most hearts.

Coburn also prepared from livers of patients who had died of rheumatic fever,

but not from livers of those who had died of other diseases, an unstable antigen which would fix complement with phase III serum to a degree parallel to the severity of the attack (this antigen also reacted non-specifically with scrums of type AB) (99) Cavelti (75), using the collodion particle agglutination technic and saline extracts of human heart as antigen, observed agglutination in 47 of 67 rheumatic serums, while in 12 normals he found none and in 84 patients with other diseases he found 1 weak and 3 doubtful positives. Those rheumatic patients who were negative were all well on the road to recovery. Almost 10 years earlier, Brokman, Brill and Freundzel (54), using complement fixation with an antigen made of liver from a child, dead of rheumatic fever, obtained positive tests in 115 of 140 acute rheumatic cases, and in only 12 of 193 controls. The so-called virus particles which were agglutinated by the patient's own serums were probably antigens similar to those discussed here. It is strange that so little interest has been accorded to these findings, which are reminiscent of early studies of the Wassermann reaction, both in results and in promise.

Other scattered observations are consistent with the hypothesis that formation of auto-antibodies underlies rheumatic fever and its congeners. Green (228) showed that fluid from the joints of acutely ill rheumatic patients would give a response resembling the Dick reaction in normal skin. Autotransplantation of joint capsular material as a method of "desensitization" has been said (449) to relieve temporarily patients with rheumatoid arthritis. Friedman, Klein and Rosenblum (206) showed that injection into convalescent rheumatic fever patients of their own serums, taken during the acute phase, produced a rise of temperature and pulse, an increase of sedimentation rate and even slight joint symptoms, while similar injections into heterologous patients had no effect. Coburn (99), by injecting scarlet fever convalescent serums, made 2 rheumatic children in the febrile phase worse and, in 18 in the afebrile phase, caused recurrence in 4. These last three results may be examples of reactivation of the rheumatic process by injection of foreign protein, and are reminiscent of the results obtained in rheumatic patients with vaccines or foreign serums. Coburn also injected phase III rheumatic serums once or repeatedly into young dogs, and observed marked electrocardiographic changes in several and gross cardiac lesions (sub-endothelial hemorrhages) in a few (99).

THE FACTOR OF SUSCEPTIBILITY

As early as 1841, a familial incidence of rheumatic fever was noted (33). In 1872, Johann Steiner of Prague described a rheumatic mother, 11 of whose 12 children had the same illness (437). In 1880, James Goodrich described 2 rheumatic parents with 5 rheumatic children (437). By 1895, Newsholme (444) was able to marshal considerable statistical material from earlier sources to show that rheumatic fever has a predilection for individual homes. He adduced this evidence in support of the thesis that rheumatic fever is an epidemic disease. In the last two decades, however, such observations have been interpreted as indicating a hereditary susceptibility to rheumatic fever. Draper (151, 152) found

37.6 per cent of 234 offspring affected in a group of rheumatic families. Benjamin (35) found 38 per cent of a group of 280 rheumatic children to have rheumatic parents and 17 per cent to have rheumatic brothers or sisters. There have been many other papers of the same nature (69, 82, 86, 94, 138, 209, 239, 240, 328, 499, 527, 573, 574, 676). An impressive example is the family described by Pickles (479), in which 24 of 53 descendants of one rheumatic individual developed rheumatic fever.

A genetic analysis by Wilson and her co-workers (678, 679, 680, 681, 682, 684, 685, 689), revealed that the susceptibility to rheumatic fever is transmitted as a single, autosomal recessive factor. They have expressed the opinion that the data of other clinicians, examined by the same statistical technique, lead to the same conclusion, and that previous workers have failed to take into account the size of the families studied and the number of parents or relatives having the disease. While many accept these conclusions (98), it is often difficult in individual studies to evaluate the relative importance of heredity and environment, as those who have a common genetic background most frequently live together and experience the same climate, housing, diet, infections and other environmental conditions. A number of workers have found, in fact, that persons from rheumatic families have, after being separated from their families, no more rheumatic attacks than those from nonrheumatic backgrounds (237, 239, 240).

The most significant detail in Wilson's studies, however, is the conclusion that not all individuals susceptible to rheumatic fever contract the disease. Of 44 children, both of whose parents were susceptible, only 86 per cent contracted rheumatic fever. This proportion, called "penetrance", probably depends upon metabolic or endocrine factors as yet poorly understood. A few facts are available which may provide a clue to the nature of the factors concerned.

No racial group appears to be unusually susceptible to rheumatic fever. Atwater (22) found a high incidence among negroes (461), but Ash (20) and others (263, 274, 592) have found a low proportion of negroes among rheumatic patients in hospitals containing equal numbers of negroes and whites. This low proportion has been explained (273) as due to the recent emigration of many negroes in the younger age groups—that is, those most affected by rheumatic fever—from the regions where these studies were conducted. Among other racial groups, no difference in susceptibility has been found (678). Further, no physical type appears to be associated with the disease (237, 678, 697).

Most workers (22, 53, 214, 532) find a slight preponderance of females over males in their rheumatic fever studies. A typical observation is that of Kaiser (320), who found 54 per cent of females among 1,200 rheumatic children. Yet a few reports (25, 73, 83) note a higher incidence in males. Since these studies, however, are based on patients in India and China, where women are given less medical attention than men, their data may be open to question.

The variation of penetrance with age is well known (462). At puberty, it decreases markedly (99, 363). In one series (53) it was observed that the preponderance of females having rheumatic fever appeared only after 20 years of age. The variation of penetrance with age is illustrated by a study of Wilson

(680, 684) who showed that the "risk" of recurrence after a rheumatic attack is 25 per cent between the ages of 4 and 13 years, 9 per cent between 14 and 16 years, and 4 per cent between 17 and 25 years

Wilson (680, 684) made another interesting observation, namely, that the risk of recurrence in the year following a major episode is twice the risk of the second year following one and three times that of the third. This is consistent with the allergic hypothesis of etiology already discussed, since many allergies vary in severity with the interval since the last previous exposure to the allergen. In this connection it may be mentioned that there are strains of animals unusually susceptible to, or unusually resistant to, certain types of sensitization (304, 361)

Rheumatic fever is rare among patients who have diabetes (26, 316), and the blood sugar has been found low in a series of patients with cardiac diseases of various types (408). Among patients who have had rheumatic fever prior to the onset of diabetes, a low incidence of characteristic cardiac involvement is found (316). A study of glucose tolerance in a series of 58 rheumatic patients showed a flat curve, of the type often labelled "functional hyperinsulinism" (591). This finding has been challenged (554, 555) and confirmed (2). Abrahamson (2) has demonstrated a functional hyperinsulinism of this type in many allergic patients, in whom suitable diet therapy reduced both the symptoms and the hyperinsulinism. Using the same treatment in a small group of rheumatic children, he was able to reduce the recurrence rate to zero over a period of two years. It is interesting that Schultz (553) could produce non-purulent carditis in rats and guinea pigs by superimposing injections of insulin and chronic focal infection.

The thyroid is presumed to affect penetrance. Exophthalmic goiter and rheumatic fever are frequently found in the same patient (99, 124). The increased metabolic rate in hyperthyroidism may well be the determining factor. Schultz (553) has shown that experimental carditis and arthritis produced by dietary means are aggravated by an increased metabolic rate. Alpern (8, 9) has increased the severity of arthritis produced by anaphylactic methods by injecting thyroxine and has decreased it by thyroidectomy. Yet Brown and Wasson (57) reported low basal metabolic rates in a group of rheumatic children. Castration does not affect experimental anaphylactic arthritis (315).

Coburn (99) pointed out that patients who have high blood lipid levels (pregnancy, diabetes, hypothyroidism, nephrosis) are most refractory to rheumatic fever. Laboratory evidence on this point is unsatisfactory, as blood lipids in rheumatic patients have been reported normal (323) as well as below normal (99, 453). Coburn (99, 104) has tested his hypothesis clinically by studying three groups of underprivileged children in New York City, 30 in each group. The first group received its customary diet, the second the same diet plus large doses of powdered egg yolk, and the third an excellent diet with various supplements. The incidence of rheumatic fever in the three groups was 38 per cent, 6.7 per cent and 5 per cent respectively. Of 20 rheumatic children given large doses of powdered egg yolk immediately after hemolytic streptococcal infections, only 1 developed a rheumatic attack, the usual incidence in this situation being 35 per cent. Coburn could not duplicate these results using para-aminobenzoic acid.

acid reinforcement or high fat diets On the other hand, low carbohydrate diets have been used by Alpern (8, 10) and by Pevsner and co-workers (477) to reduce the severity of anaphylactic types of arthritis

If penetrance is affected by other metabolic factors, the fact is not reflected in any of the usually performed laboratory tests The lipoids and crystalloids of the blood remain normal in rheumatic fever (100, 323, 554, 556). In the urine during the acute phase, indole (192) and increased coproporphyrin (326) have been found, presumably as a result of hepatic damage accompanying an acute febrile episode The hemorrhagic tendency frequently present has been ascribed (384) to hypoprothrombinemia from the same cause In patients having acute chorea, there is an increased excitability of the neuro-muscular junction (74) and the concentrations of calcium in the serum and cerebrospinal fluid are significantly lower than in recovered patients and controls (652) This finding has prompted the therapeutic use of calcium in chorea with reputedly good results (439)

The few changes known to occur in acute rheumatic fever can be referred largely to the streptococcal infection usually preceding or accompanying the attack Among these changes may be included the increased leukocyte count, the low platelet count (657), the disappearance of the eosinophils (205, 611) and the rising sedimentation rate (it remains normal in chorea (172)) The increased sedimentation rate, in turn, has been shown to be associated with a rise of α_1 and α_2 globulins and fibrinogen (100, 148, 535, 575, 593) The gamma globulin parallels the rising antistreptolysin-O titer (148, 535, 575) In a study of 6 cases of scarlet fever (148, cf also 496, 598), the electrophoretic serum patterns of 3 in whom rheumatic fever developed, differed in no way from those of the 3 in whom rheumatic fever did not develop The Weltmann serum coagulation reaction has also been shown to parallel alpha globulin changes, and is found more frequently in the presence of clinical rheumatic activity than is an increased sedimentation rate (543, 544, 651). The formol-gel test seems to have little direct correlation with the activity of the rheumatic process (68, 339), and the so-called Mester test (419) appears to have no specificity for rheumatic fever (52, 128, 694) The complement in the blood of rheumatic fever patients has been shown by several workers (63, 96, 139, 295, 490, 549, 641) to be diminished during the acute phase, as it is in nephritis (250, 333, 501, 641), an observation usually interpreted as demonstrating the combination of antigen and antibody within the organism (63) However, a recent study (188) throws this point into doubt (255)

THE FACTOR OF DIETARY DEFICIENCY

The possible effects of certain dietary deficiencies on penetrance have been mentioned briefly The dietary constituent, however, which for a number of years received the greatest attention as related to the etiology of rheumatic fever was ascorbic acid It is discussed here as an example of the rise and fall of a hypothesis The type of evidence used to support it differed little if at all from that used in defense of currently favored hypotheses, and its demise was brought

about by observations quite analogous to others which can be urged in opposition to many of the hypotheses of today

In 1932, Rinehart and co-workers (509, 513, 516), induced chronic scurvy in guinea pigs, superimposed an infection with streptococci or other organisms and thereby produced fibrinoid changes in the periarticular tissues which resembled those described by Klinge (344) as the essential lesion of rheumatic fever. This finding was confirmed (510), although Asehoff (17) and other workers (551) believed that the lesions were not those of rheumatic fever. The point was made by Schultz (553) that duplication of the correct pathologic mechanism in an experimental animal might yet give a pathologic picture different from that in human beings. Rinehart pointed out that rheumatic fever is rare in the tropics where the average diet is high in antiscorbutic potency (523), has its greatest incidence between the ages of 5 and 15 years when the vitamin C requirement of children is at its greatest (177), and occurs most frequently when the supply of vitamin C is lowest (177). He suggested that the symptoms of early rheumatic fever and latent scurvy, as described by some authors, are very similar. These facts were also consistent with the hypothesis that rheumatic fever is an infectious disease or secondary to an infectious disease, and thus lacked conviction.

In later work, Rinehart and co-workers (514, 515) found the plasma level of ascorbic acid in cases of acute rheumatic fever to be significantly lower than in normal subjects or in patients who had non-rheumatic diseases. This too was confirmed (280, 282, 489), and a low excretion of vitamin C was observed, even in patients receiving an ample supply of the vitamin (1, 280, 559). Increased capillary fragility, presumed to be a sign of latent scurvy (more recently interpreted as an indication of streptococcal toxicity (55, 134)), was found in many or all rheumatic children in various phases of the disease (56, 58, 470, 657).

Rinehart abandoned his hypothesis (511) in 1943, because of the following evidence: (1) Ascorbic acid blood levels are considerably decreased in a variety of diseases (66, 186, 526, 550), especially in the presence of fever (65, 260). (2) There is an inverse relationship between temperature and excretion of ascorbic acid (550), even electrically induced fever for two to five hours suffices to lower blood and urine levels markedly (131). (3) Massive doses of vitamin C failed to change the clinical course of rheumatic attacks (355, 552, 695) and were unsuccessful in raising the low plasma level of vitamin C (552). Such doses caused a marked reticulocyte response in some cases (179).

As there is some evidence that rheumatic fever may involve an abnormal activity of the immune mechanism, one should note that vitamin C unsaturation has been found in cases of urticaria (526), sensitivity to salicylates (468), and asthma (223). Experimentally, cutaneous sensitivity to neoarsphenamine is increased by vitamin C deficiency (84, 596), anaphylaxis is reported to be less (491) or more (586) severe in vitamin C deficient animals, the tuberculin reaction is decreased in sensitized animals deficient in vitamin C (234, 488), tissue ascorbic acid levels are lower in scorbutic animals when sensitized to horse serum or shocked anaphylactically (145), antibody production in vitamin C deficient rab-

bits and guinea pigs is lower than in controls (391, 491), and ascorbic acid is necessary to the formation of complement (160, 161, 162). Tuberculosis, to which rheumatic fever shows some analogy in its clinical-pathologic characteristics, is noted for its low levels of vitamin C in plasma and urine (82, 211, 275, 307, 325). Furthermore, vitamin C has been reputed to be of value in the prophylaxis (406) and treatment (405) of certain types of tuberculosis. Tuberculosis progresses more rapidly in scorbutic animals than in controls (234, 407). In the absence of more adequate information, these observations may be interpreted as favoring or opposing the concept of rheumatic fever as an allergic disease, according to one's individual bias.

Other vitamins than ascorbic acid have received attention as perhaps connected in some way with the rheumatic process. Rinehart (511, 512) has recently used hesperidin or vitamin P in a small series of patients whose rheumatism was persistently active. He expressed the opinion that the clinical improvement observed warrants further investigation. Low plasma levels of vitamin A have been observed in rheumatic patients (282, 489, 572), but no curative effect has resulted from large doses of A, B, or D (308, 355). Deficiencies in these substances also result in deficient immune responses (433) (see Werkman (667) for opposed view). Pevsner and his co-workers (477), who look on rheumatic fever as a form of anaphylaxis, have shown, using horse serum in dogs and rats, that a high carbohydrate diet increased the intensity of the Arthus reaction while a vitamin D deficient diet caused it to disappear. A few papers appear from time to time reporting excellent therapeutic results in rheumatic fever from some specific diet (560, 642, cf. 366), often with rather obscure rationale. Dvorak used vitamin D₂, reasoning from the formal chemical relationship of digitalis glucosides to antirachitic vitamins that the rheumatic heart injury must be due to the effect of an unknown inflammation on a calcium-poor substrate (154).

It is difficult to evaluate the role in rheumatic fever of such a complex of factors as the average diet. Yet there remains good evidence (see also the preceding section) that dietary inadequacies may affect the penetrance or incidence of rheumatic fever (303). This evidence has been reviewed by Peete (467), who pointed out the low incidence of this disease in people who eat fish oils and high protein diets and in farm states as compared with industrial or cotton and tobacco states. He reviewed the by now well-recognized relation of both rheumatic fever and diet to climate, season, geography, age and other factors. Unfortunately, dietary inadequacies, shown in almost every epidemiologic study to be correlated with the incidence of rheumatic fever, are also correlated with poor housing and clothing, low economic status, crowding and deficient hygiene, conditions which may affect penetrance in other ways.

HYALURONIDASE AND HYALURONIC ACID

A good deal of attention has centered lately on hyaluronic acid and the various enzymes that act on it, known collectively as hyaluronidase (for a recent review, see 422). Hyaluronic acid is a mucopolysaccharide which has been isolated

from skin, synovial fluid, mesenchymal tumors, vitreous humor and umbilical cord, and which is suspected of being an important constituent of the amorphous ground substance of connective tissue (289, 421, 422, 423, 424, 425, 703) It has been extensively studied by Meyer and his group, and is better understood than other perhaps equally important mucopolysaccharides (421, 703h) Yet certain details of its structure remain in considerable doubt, it is not even known upon what linkages the various hyaluronidases act, nor to what breakdown products they give rise (703h) These substances are in most cases apparently mixtures of several enzymes, and have different actions on different substrates (425, 703) They may be obtained from streptococci, staphylococci, pneumococci, or *Clostridium welchii*, from testicular tissue, or from certain other tissues such as aqueous humor (424, 425, 480, 703j) They do not affect collagen (Gross in discussion, 703e)

The interest of these substances for the student of rheumatic fever is based on four facts hyaluronic acid is an important constituent of the connective tissue, the seat of the rheumatic process, hemolytic streptococci produce hyaluronic acid and hyaluronidase, hyaluronidase causes in the skin of rheumatic patients spreading reactions which may be inhibited by salicylates, and finally hyaluronic acid raises the sedimentation rate in vivo and in vitro, whereas hyaluronidase lowers it, even in rheumatic patients (704)

The presence of hyaluronic acid in the connective tissue, far from being an established fact, is not known at present from any direct evidence (422, 703h) It has been inferred from the spreading activity of hyaluronidase (discussed later in this section) and from the presence of metachromatic staining material throughout the connective tissue (423, 703a, 703h) This staining reaction is given by each of the mucopolysaccharides (421) If it is abolished by treating tissue with hyaluronidase before the stain is applied, one may conjecture that the stained material is hyaluronic acid However, testicular hyaluronidase also depolymerizes chondroitin sulfate, which may therefore be mistaken for hyaluronic acid by the use of this method Bunting has shown (703a) that in synovial fluid and Wharton's jelly, the metachromasia is removed by both testicular and streptococcal hyaluronidase, whereas in a number of connective tissues, only testicular enzyme will affect it Of the tissues from which hyaluronic acid has actually been isolated, namely the skin, umbilical cord, synovial fluid, and vitreous humor, only the skin is involved in the rheumatic process The hyaluronic acid in synovial fluid has been shown (423, 428, Ragan in 704, Ropes in 704, 703i) to be considerably depolymerized in rheumatoid arthritis Ragan and Meyer (704, 703i) choose to look upon the joint space as an interfibrillar connective tissue space, and view this change in the synovial hyaluronic acid as evidence of an abnormality of the ground substance in other regions of the connective tissue

The production of hyaluronidase by streptococci is also an argument of less strength than appears at first Although under appropriate conditions most group A hemolytic streptococci will produce hyaluronidase (703j), it is usually unencapsulated (130, 561, 562) organisms that do so (since the capsule consists

of hyaluronic acid (480, 481, 482)) On the other hand, the streptococci involved in the infections preceding rheumatic exacerbations are usually encapsulated and virulent (483) Kuttner observed an outbreak of sore throat due to type 4 streptococci (types 4 and 22 are the only types commonly producing hyaluronidase in large quantities) in a home for rheumatic children, with no consequent rheumatic recrudescences (quoted in 428, and 703i) Streptococci of group C, which also produce this enzyme, as well as hyaluronic acid (428, 561), are likewise not implicated in the disease Hyaluronidase may even be used to combat infections with virulent organisms (327, 533, 404 contra) It should be emphasized that the peak of the streptococcal attack is the time when the individual is exposed to the greatest amounts of hyaluronidase, yet it does not coincide with the peak of the rheumatic attack, which may follow it by several weeks

With these considerations in mind, one must accept with caution any hypothesis based on the study of substances in human serum which will inhibit hyaluronidase (153, 207, 217, 251, 289, 404, 703c, 703d, 703f) It is important to distinguish in any particular study whether testicular or streptococcal hyaluronidase was used, since there are two different inhibitors, which differ considerably in their properties The inhibitor of testicular hyaluronidase is heat labile and appears in the albumin fraction of serum (217, Harris in discussion, 703) The other is found among the gamma globulins and is stable at 56°C (703c, 703d, 265a) The former was named by Haas antinvasin I (he also described a proinvasin I and antinvasin II) (251, 252, 253) McClean (404) and Haas (251) found this inhibitor in serums of many animal species, Hobby et al (289) concluded that it was not an antibody Kinetic studies of its reaction with bovine testicular hyaluronidase did not support the suggestion that it is an enzyme (422, 703c), though magnesium was necessary for its activity (Meyer states that no magnesium is required if perfectly pure hyaluronic acid is used as a test substrate (discussion, 703) Both Haas and Dorfman have found this inhibitor decreased in the serums of patients with acute rheumatic fever, as well as in other diseases (251) The latter advances the hypothesis that the streptococcal infection, by introducing considerable hyaluronic acid into the patient's tissue, stimulates the production of his own hyaluronidases or the lowering of his inhibitor levels to permit greater hyaluronidase activity, even perhaps in the connective tissue

The inhibitor to streptococcal hyaluronidase, on the other hand, is increased in rheumatic fever Friou and Wenner (207), Friou and Quinn (703d) and Harris (265a) have found it increased to a similar or greater degree than that in the blood of patients who recently have had scarlet fever It reaches its maximum in 2 to 4 weeks after the onset of the streptococcal infection, but is not present in every rheumatic case (Friou in discussion, 703) It may well prove to be another in the long list of antibodies to streptococcal products It is not effective against the hyaluronidases produced by streptococci of groups B, C, or D Both this and the inhibitor of testicular hyaluronidase were shown by suitable controls not to be identical with salicylate Hechter states that the

inhibitor is ineffective in preventing spreading activity, at least in the case of testicular hyaluronidase (discussion, 703)

Hyaluronidase has long been identified as a so called "spreading factor" (153, 289, 423, 424). However, the spreading activity of a particular substance has been shown by Hechter (703g) to depend on the local intercellular pressure as influenced both by the volume injected and the amount of local edema fluid, if the substance is an agent damaging to capillaries. An understanding of this point is necessary for a proper interpretation of the findings of Guerra (246, 247, 248, 249). He found that the spreading of India ink when injected with hyaluronidase into rabbit or normal human skin could be inhibited from 57 to 66 per cent by oral or intravenous administration of salicylates. In the skin of rheumatic patients, the ink spread widely. This spread was inhibited by salicylates. Ragan and Harris (discussion, 703) both state that they have been unable to confirm this observation. Guerra obtained a similar result in a normal individual.

The effect of salicylates on spreading due to hyaluronidase is interesting and suggestive, and has been amply confirmed (428, 703i, 703j). Yet the concentration necessary *in vitro* to inhibit the enzyme is such as to denature proteins (427, 428). On the other hand, gentisic acid, a metabolic product of salicylic acid, will inhibit hyaluronidase in low concentrations *in vitro* while acting as a powerful antirheumatic agent *in vivo* (427, 428). A further oxidation product, carboxy-p-benzoquinone (382) is also said to be effective *in vitro*. Meyer states that an oxidation product rather than pure gentisic acid is the effective agent and that a variety of related quinones and hydroquinones have the same type of inhibitory activity (discussion, 703). It is pointed out by Hechter that available information makes it impossible to judge to what degree the effects on spreading of these various substances is dependent on actual inhibition of hyaluronidase rather than on other mechanisms, such for example as an effect on interstitial fluid content (discussion, 703).

As for the last of the four points, the increased sedimentation rate, produced by hyaluronic acid preparations, has been shown by Ragan (422) to be associated with spherocytosis, which does not exist in rheumatic fever, and the ability of hyaluronidase to lower the elevated rate does not depend on its ability to split hyaluronic acid (422, Meyer in 704). A variety of macromolecular materials can elevate the sedimentation rate, as for example gelatin, agar and pneumococcus III polysaccharide (699, 704). Youngner and Altshuler (698) examined the blood of a number of patients with rheumatic fever, rheumatoid arthritis, lupus erythematosus, tuberculosis and Hodgkin's disease and showed that there was no hyaluronic acid in the blood to account for the increased sedimentation rate.

A speculative point is the possibility that during the initiating infection the hyaluronic acid in the capsule of the invading streptococci may act as a hapten, much as do pneumococcus polysaccharides, and may give rise to formation in the patients of antibodies to hyaluronic acid, a constituent of their own tissues. Schultz and Rose (558) have produced particularly potent "bacterioplasm"

conjugates" using umbilical cord extract and hemolytic streptococci. Yet as far as is known, hyaluronic acid is not antigenic alone and does not act as a hapten in experimental infections with mucoid hemolytic streptococci (334, 561, 374 contra). A material produced by coupling hyaluronic acid to horse serum albumin was not antigenic in rabbits (298).

This discussion should be concluded by calling attention to the existence of other connective tissue constituents which have been almost forgotten in the enthusiasm surrounding the recent work on hyaluronic acid and its enzymes (340). Chondroitin sulfate (421, 423) and collagen (324, 354) are substances about whose presence in the involved tissue there is little doubt. Elastin, reticulin, and other less well understood materials likewise are present in connective tissue. Collagen is now receiving some attention as a possible participant in the disease process of rheumatic fever (Gross in 704 and 703e). There is available for purposes of study an enzyme which attacks it (174, 452). In the only study of its antigenicity known to the reviewer, whole rat tail tendon, which contains many other substances, was used as the antigen (377). Gelatin, its denaturation product, is not antigenic (590). Chondroitin sulfate, which, as Meyer suggests, may act as the cement substance between connective tissue fibrils (421, 423), easily forms complexes with proteins (423), in which form it appears to exist normally (703h). Its antigenicity has not been studied. It is hydrolyzed by certain hyaluronidases (428, 703h). The capillary cement substance has hardly been studied, though of primary importance in all questions concerning connective tissue. Chambers and Zweifach (703b) have shown that testicular hyaluronidase does not affect this material though it apparently does weaken the capillary wall.

OTHER FACTORS

Speransky and others (224, 587) have adduced evidence to show that rheumatic fever, like many other diseases, though showing manifestations usually accepted as inflammatory, is part of a generalized neurodystrophic process. This hypothesis was applied to rheumatic fever because no specific etiologic agent had been found and also because the sequence of appearance of the successive involvements of joints suggested the spread, at first segmentary and later generalized, of known clinical and experimental neurodystrophies. Lichtwitz (368), in the United States, was impressed by the same type of evidence. Speransky obtained reputedly good therapeutic results by use of his spinal pumping method simultaneous with oral salicylate therapy. This finding has been confirmed by Gillman and Gillman (215), but it should be noted that both groups of workers mixed cases of rheumatoid arthritis and cases of rheumatic fever indiscriminately. Non-specific peripheral vascular effects were observed after the pumping, which probably caused the clinical improvement claimed (49, 541). Unilateral sympathectomy causes marked changes in the character of experimentally induced arthritis (8, 9).

Another technic has been developed by Selye and his associates (566, 568, 570) in experimental animals sensitized by high salt intake and unilateral nephrectomy.

and given doses of adrenal cortical hormone or pituitary corticotrophin, or exposed to cold or some other damaging agent. Many of these animals showed migrating polyarthritis (469) resembling rheumatic fever and later developed permanent joint damage suggestive of rheumatoid arthritis. Lesions resembling periarthritis nodosa, rheumatic fever in the heart and malignant nephrosclerosis have been reported. There is no need here to discuss Selye's work (565) in detail, with its new nomenclature which contains descriptive terms such as "adaptation syndrome", "alarm reaction", "stage of resistance", "stage of exhaustion", "catabolic impulse", and so forth. It is postulated that damaging agents stimulate pituitary production of corticotrophin, which in turn stimulates the adrenal cortex. Some of the changes observed can be shown to depend on one or the other of these two secretions. Step one of the process is influenced markedly by protein intake, step two by salt (149, 272, 569). The etiologic hypothesis suggested by these observations would make rheumatic fever an example of the alarm reaction following various precipitating events. It remains to be explained why not all individuals respond in this manner to such events. On the other hand this hypothesis is consistent with the observation that a variety of events such as, infection, cold, trauma and fatigue, may precipitate rheumatic attacks.

It is also possible that adrenal cortical secretion, which is said (85, 672, 296 *contra*) to have a marked enhancing effect on antibody production, may raise the titre of auto-antibodies usually present at too low a level to damage tissue.

THE CRITERIA OF RHEUMATIC FEVER

For a more comprehensive understanding of the present status of research on rheumatic fever, it is necessary to consider briefly the relationship between the morphologic changes in rheumatic fever, those in other diseases, and those induced by various means in experimental animals. Because the clinical picture of rheumatic fever is so frequently indeterminate, many efforts have been made to determine some laboratory finding characteristic of the disease (see the discussion of sedimentation rate, Weltmann reaction, Mester test, formol-gel test, and other blood changes). The only well-defined characteristic of rheumatic fever is its pathologic picture.

There are many excellent reviews describing the histologic changes of rheumatic fever (227, 241, 242, 618, 619, 643, 346). A most thorough study of Aschoff bodies in their relation to the disease process was carried out by Gross and Ehrlich (241, 242). They classified the lesions on the basis of the appearance and distribution of the collagen, the argentophile reticulum fibers, the cell nuclei, and their cytoplasm, into seven types. Each was specific and each occupied a definite position in the life cycle of the lesion. Although they felt that no single component of the Aschoff body was sufficiently characteristic to identify the lesion, the combination of swollen and fragmented collagen, a basket-like argentophile network, polymorphous cells with ragged edges, giant cells of the specific type described, and varying proportions of pyknotic, fibrocytoid, and large owl-eyed nuclei sufficed to distinguish this lesion from that of other diseases.

Other outstanding studies of the Aschoff body have been made by Clawson (91), Talalaeff (618, 619), Graff (226), Von Glahn (643), and others (62, 537). Klinge (345, 346, 347) is regarded by many as the definitive student of the pathology of this disease. The lesions have been described as occurring not only throughout the heart and great vessels (62, 537), but also throughout the body (110, 345, 353, 601, 602, 603, 604, 643), even in the central nervous system (59, 225, 335, 643) and skin (331, 383)

The real disagreement, however, has concerned not so much the complete Aschoff body as the primary change which is believed to precede it. Von Glahn and Pappenheimer (644) expressed the belief that the primary lesion, like the lesions of periarteritis nodosa, is in the walls of blood vessels. Klinge (344) found that the lesions began with a fibrinoid degeneration of collagenous connective tissue. Masugi and co-workers (403) thought that the proliferative lesion appeared frequently without any evident preceding fibrinoid change. Aschoff (17) believes that the importance of collagen necrosis as the primary change is exaggerated by Klinge and his school. In Coburn's opinion (98), the rheumatic process involves primarily the mucoprotein cement substance of blood vessels and secondarily the endothelial and subendothelial cells and the collagen, the proliferative change would be tertiary. This disagreement is particularly important because few lesions produced in experimental animals have resembled the full-blown Aschoff nodule as described by Gross and Ehrlich (241). More often they have consisted of collagen necrosis followed by relatively non-specific cellular proliferations. It is doubtful (62, 242, 340, 519, Klempeier in 704) whether collagen necrosis alone is specific to a degree justifying the claim that such lesions are those of rheumatic fever, since it is found in unrelated diseases (340, 341, 691)

There is also disagreement regarding the origin of the Aschoff cells, some maintaining that they are derived from histiocytes (91), others that they are modified "Amitschkow" myocytes (92), still others that these myocytes are a local variety of histiocyte (170). The responsible cell outside the heart has been studied in vitro with vital stains (409). In the cellular content of various exudates (410) and transudates, evidence has been found to justify including rheumatic fever with others of Bergstrand's "allergic granuloma" group (673)

The Aschoff body may not be as specific for rheumatic fever (403, 540) as is thought. It has been found in cases of infectious diseases (91), scarlet fever and tuberculosis (400, 401, 403). Masugi and co-workers (400, 436) found a frequent association between rheumatic fever and tuberculosis and thought that they could demonstrate all gradations between the tubercle and the Aschoff body. Yet the incidence of positive tuberculin reactivity is the same in rheumatic patients as in normal persons (166, 459). In this connection, erythema nodosum (376, 580) was originally considered a manifestation of rheumatic fever (386). It now appears that there is little basis (283, 331, 474) for this assumption. Wallgren (648, 649) concluded that this disease is associated with either rheumatic fever or tuberculosis. Spink (589), using beta streptococcus nucleoprotein in some cases and tuberculin in others for intradermal injection, was able to

produce in patients with erythema nodosum the typical lesions of that disease. Erythema nodosum is also found (176) with coccidioidomycosis, a disease closely analogous to tuberculosis. Barber (27) has attempted to show how the cutaneous manifestations of rheumatic fever resemble, point by point, the corresponding, presumably allergic, cutaneous manifestations of tuberculosis. The behaviour of the eosinophils and the sedimentation rate in tuberculosis is much like that in rheumatic fever (39, 202), and some workers (375) actually consider rheumatic fever to be a manifestation of tuberculosis. The importance of these observations lies in the analogy which appears to exist between the two diseases (461) and which becomes understandable in terms of the hypothesis of allergy in rheumatic fever.

The cutaneous and articular lesions of rheumatic fever were thought by Klinge and Grzimek (348) to be sufficiently like those of rheumatoid arthritis to justify calling them the same disease. This opinion was substantiated by Dawson (135) and by Fisher (191), but has been opposed by Collins (120) and by others (17, 18, 19, 37), who found different histologic sequences in the two types of lesions. Dawson and Tyson (138) collected a mass of data supporting the idea that the two diseases are closely related to each other, if not the same process in different age groups. They pointed out that rheumatoid arthritis appears to be hereditary and that rheumatic fever frequently occurs in families in which rheumatoid arthritis is also present (14 per cent in their series and 32 per cent in that of Coates (94)). They mentioned that rheumatoid arthritis is rare in the tropics (88), that it frequently follows respiratory infections which having a maximal incidence in March, and that endocarditis does occur, especially in cases with an early onset.

It has been noted that rheumatoid arthritis and rheumatic fever appear together in certain families (163, 168). Apparently streptococcal and other infections precipitate attacks of this disease (164). Trauma also has an analogous role (165, 168). Ceel and co-workers (80) isolated from the joints and blood of rheumatoid arthritic patients organisms similar to those that he had found in rheumatic fever. It is generally agreed that agglutinins to hemolytic streptococci are increased in this disease (15, 67, 137, 411, 447, 647), whereas antifibrinolysin and antistreptolysin remain normal (44, 67, 411, 441, 472, 702). This antibody picture is explained by the fact that rheumatoid arthritis is a chronic disease. Dawson and Tyson's argument concerning age is weakened by the occurrence of rheumatoid arthritis in childhood (129, 168) and the not infrequent occurrence of rheumatic fever in old age (132, 140, 141). Adult migrants from Puerto Rico to New York acquire typical childhood rheumatic fever (138). On the other hand, cases intermediate between the two diseases have been described (146, 168). Chronic joint changes have been observed (98, 189, 201) to follow typical rheumatic fever. In fact it is customary in some European countries to consider that all intermediate gradations exist clinically.

Convincing evidence is provided by studies of heart disease in rheumatoid arthritis (16, 31, 36, 37, 87, 129, 168, 180, 185, 190, 208, 245, 283, 492, 522, 524, 696). One series of 38 cases of rheumatoid arthritis in which autopsy was per-

formed included 25 cases (65.8 per cent) with typical rheumatic heart lesions (696). Kahlmeter (318), studied 65 cases of acute rheumatic fever, 106 of subacute rheumatic fever, 37 of secondary chronic arthritis (what we would call acute or subacute rheumatoid arthritis), and 48 of primary chronic arthritis. He found clinical and electrocardiographic changes in the second and third groups quite comparable with the first, while the primary chronic arthritis had no more lesions than infectious disease controls. Hench and co-workers (525) at the Mayo Clinic, however, studying 147 cases of proved rheumatoid arthritis and 100 controls by auscultation, blood pressure measurement, roentgenograms and electrocardiography (using Katz's liberal standards for normal), found no difference between the two groups, in spite of the fact, established by several groups of workers, that 26 to 65 per cent of such patients are found postmortem to have typical rheumatic cardiac lesions.

These findings are countered by an interesting observation of Hall and Anderson (257, 258) and confirmed by Karsner (258), that microscopic stigmata of rheumatic heart disease (vascular changes, fibrinoid swelling, Aschoff nodules and interstitial infiltration) are present in approximately 90 per cent of supposedly normal hearts. They interpreted these as allergic hyperergic responses in relatively immune persons to the "virus" of rheumatic fever—be it recurrent upper respiratory infection or streptococcal infection—comparable to the widespread immunities to tuberculosis and poliomyelitis. This is in keeping with Mallory and Keefer's finding (395) that the hearts of patients dying of various types of streptococcal infection show focal changes, possibly related to Aschoff nodules. It is believed by Hench and his colleagues (283) that the lesions observed by Hall and Anderson are "non-specific tissue responses to various insults, not necessarily to the 'rheumatic virus'." Another suggestive observation is that of Kaiser (322), who described a common clinical syndrome resembling rheumatic fever but easily cured, having few recurrences and infrequent sequelae. Watson and colleagues (659) showed that in a certain number of cases of scarlet fever, while symptoms are not apparent during convalescence, electrocardiographic changes develop comparable to those appearing in patients who have rheumatic fever. If the cases thus described are accepted as constituting a clinical entity, there appears to exist a complete "spectrum" of illnesses of the rheumatic or rheumatoid type, ranging from asymptomatic cases or those with mild "growing pains" (269), anorexia, fatigue, pallor, irritability, headache, abdominal symptoms and slight fever, at one extreme to severe, crippling rheumatoid arthritis of insidious onset at the other. Possibly all are manifestations of the same fundamental disturbance with modifications imposed by as yet unknown factors. It is suggested that differences result from differences in the antigens concerned (650).

Other diseases too have been identified with rheumatic fever. The suggestion that there might be a connection between it and *periarteritis nodosa* was considered by Spiegel (588) and by Friedberg and Gross (203). This point has been emphasized by Rich (504). Friedberg and Gross concluded that the vascular lesions of the two diseases were not the same (confirmed by Masugi and Isibasi (399)) but that their frequent association might explain occasional cases of

abdominal rheumatic fever, such as those of Langmann (361) It is interesting to note that several of the experimental techniques for inducing rheumatic fever in animals produce changes which resemble periarteritis nodosa In regard to subacute bacterial endocarditis, which resembles the lesions obtained by early experimenters with intravenous injections of streptococci, Von Glahn and Pappenheimer (645), and Masugi and Isibasi (399) have shown that the streptococci implant on the lesions of rheumatic fever

There is little need to re-emphasize the dangers of drawing conclusions from animal experiments alone Several methods have been supposed by their proponents to produce lesions in animals which resemble those of rheumatic fever As early as 1884, Loeffler (372) induced suppurative arthritis in 9 of 12 rabbits by intravenous injection of streptococci obtained from patients with scarlet fever or diphtheria In 1893, Triboulet and Coyon (634) produced mitral endocarditis in rabbits with diplococci isolated from patients who had rheumatic fever In 1904, Cole (118) and Harris (262) showed that any streptococcus would cause joint lesions in experimental animals In 1921, Topley and Weir (631) described these lesions and distinguished them carefully from those of rheumatic fever Yet several papers have appeared since (80, 84, 93, 582), which claim the production of rheumatic lesions by injection of organisms obtained from rheumatic patients

The allergic or anaphylactic technique, already described, has given a pathologic picture considerably closer to that of rheumatic fever The changes produced by focal infections with relatively avirulent streptococci (12, 393, 398, 700), including those produced by Rinehart's technique (509, 513, 553), would seem to belong in this category In 1936, Vaciera (638), examined all the methods in vogue (393) for the experimental production of "rheumatic fever" and controlled his findings with slides obtained from Aschoff, Fahr, and Graff He concluded that rheumatic fever had yet to be duplicated, that arthrophilic streptococci did not exist, and that the monocytic histiocytic nodule produced by "allergic" methods could also be produced in other ways and was not exclusively rheumatic It is difficult at this point to classify the lesions obtained by MacNeal and co-workers (388, 389, 390) and by Selye and co-workers (568, 570) There are some investigators (519, 200) who are unwilling to label the lesions which they have obtained experimentally as rheumatic fever It is necessary to remember that any colloidal material given intravenously in large quantities causes a cellular response in various organs not too dissimilar from the lesions under discussion (450) The picture is complicated by the fact that cardiac and vascular lesions resembling those of rheumatic fever are reported to occur spontaneously in rabbits, rats, and mice (195, 300, 362, 373, 431, 674, 675) Perhaps the true pathologic mechanism has been duplicated by one of the procedures described, it appears that the pathologic picture has not (17, 643)

SUMMARY AND CONCLUSIONS

Susceptibility to rheumatic fever is a hereditary factor, though the same pathologic process seems to take place to a limited extent in many normal persons The frequency with which susceptible individuals contract rheumatic

fever, the so-called penetrance, is influenced both by internal factors such as sex, age, pregnancy, diabetes and thyroid disease, and perhaps others as yet undetermined, and by external factors such as climate and diet

Pathologic similarities and overlapping heredity and incidence suggest similar defects in rheumatic fever, rheumatoid arthritis, periarthritis nodosa and glomerulonephritis. This suggestion is confirmed by the simultaneous production in one animal of what appear to be two or even three of these diseases by one experimental technic

Rheumatic patients show a marked non-specific hyperirritability to most stimuli. Attacks of rheumatic fever are usually precipitated by streptococcal throat infections, though trauma, cold and fatigue may also initiate attacks. What process is set in motion by these various events is not known, it may be the adaptation syndrome of Selye, a non-specific allergic response, an increasing titer of auto-antibodies against some constituent of connective tissue or even the reactivation of a latent virus infection. The second and third of these alternatives are strongly supported by a number of observations

There is no evidence that hyaluronidase plays a role in the pathogenesis of rheumatic fever, but hyaluronic acid may

The clinical pattern of rheumatic fever may depend on such factors as trauma, environment, previous rheumatic history, and conceivably nervous reflex patterns

No measurable change has been found in rheumatic fever, to serve as a diagnostic tool and as a starting point for research, except for postmortem histologic changes

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For exhaustive reviews of the literature since 1934, consult Hench and others (276) to (283) For literature between 1939 and 1945, see Perry (475)

PULMONARY INSUFFICIENCY

III A STUDY OF 122 CASES OF CHRONIC PULMONARY EMPHYSEMA¹

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INTRODUCTION

In this paper, the third of a series dealing with the problem of pulmonary insufficiency, various types of pulmonary dysfunction observed in chronic pulmonary emphysema are described and discussed

Some of the physiological disturbances resulting from the development of chronic pulmonary emphysema have been studied in a limited number of investigations during the past twenty years. Loeschcke⁽¹⁾ and Christie⁽²⁾ emphasized the mechanical aspects of the disease, pointing out respectively the role of chest deformity and of the loss of lung elasticity demonstrated by intrapleural pressure measurements, in reducing the efficiency of respiratory movements. A major contribution to the study of pulmonary function in emphysema was made by Knipping in 1932 (3, 4).⁽³⁾ This author and his school considered the various mechanisms causing a reduction in arterial blood O₂ saturation. He described two main causes of arterial anoxemia: 1) the limitation of the maximum breathing capacity (atemgrenzwert) to such an extent that it restricts ventilation during increased physical activity, and 2) the lack of correlation between alveolar ventilation and perfusion. However, it was only after the development of methods for the study of intrapulmonary distribution of respiratory gases by Sonne, Nielsen and Roelsen (5, 6, 7) and Darling et al (8) that data were obtained which confirmed the latter mechanism by demonstrating unequal ventilation in different parts of emphysematous lungs. In his studies Knipping also called attention to a syndrome characterized by hypoventilation associated with gaseous acidosis, a high CO₂ content and a low oxygen saturation in the arterial blood. This syndrome, observed mainly in cases of narcotic overdosage, was also seen in patients with chronic pulmonary and circulatory insufficiency. The cases described as "cardiacos negros" by Berconsky (9) would seem to belong to this particular group. They showed clinical evidence of severe pulmonary emphysema and of cardiac failure associated with polycythemia, plethora and cyanosis, and the physiological pattern described was characterized also by hypoventilation, marked arterial anoxia and an elevated carbon dioxide tension.

The more recent contribution to the physiopathology of chronic pulmonary emphysema by Hurtado, Kaltreider, McCann and other members of the Rochester group (10, 11, 12) is also of particular interest. These authors demon-

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strated a good correlation between the degree of arterial blood O_2 unsaturation and the degree of pulmonary emphysema as measured by the increase in the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$. They stressed also the importance of physical exercise in causing hyperventilation and in reducing to a very low level a breathing reserve already greatly restricted by a low maximum breathing capacity.

In the present paper we shall describe and attempt to classify the more prevalent forms of physiological disturbance encountered in chronic pulmonary emphysema, to indicate in certain cases the natural history of this disease, and to discuss how its course may be influenced by therapeutic measures.

MATERIAL FOR STUDY AND CLASSIFICATION

The cases for this series were selected from a large group of patients with chronic pulmonary disease, on whom functional studies were performed, on the basis of the following criteria:

- 1 The presence of clinical and x-ray evidence of pulmonary emphysema
- 2 A residual air greater than the predicted value and contributing at least 36% to the total lung volume

Cases with large pulmonary air cysts or bullae were excluded and will be presented in a subsequent paper.

One hundred and twenty-two cases met these requirements and were partially or completely studied using the methods described and analyzed in the first paper of this series. Of this entire group sixty-eight patients were completely studied with respect to their arterial blood gases and form the statistical basis of this report. Fourteen patients were followed with repeated observations over a period of one to thirteen years.

The one hundred and twenty-two cases may be divided into two main categories on the basis of clinical and roentgenological data:

I Uncomplicated pulmonary insufficiency

This group consists of one hundred and three cases with no clinical evidence of congestive heart failure or roentgenological evidence of cardiac enlargement.

The cases belonging to this first category were further divided into the three following groups according to the presence or absence of arterial oxygen unsaturation and carbon dioxide retention following the standard exercise test.

Group 1 with an arterial oxygen saturation above 92 per cent following the standard exercise test

Group 2 with an oxygen saturation and a carbon dioxide tension in the arterial blood respectively below 92 per cent and below 48 millimeters of mercury, following the standard exercise test

Group 3 with an arterial oxygen saturation below 92 per cent and a carbon dioxide tension above 48 millimeters of mercury following the standard exercise test

II Combined cardio-pulmonary insufficiency

This group (*Group 4*) consists of nineteen cases with clinical evidence of cardiac enlargement and dilatation of the pulmonary arteries.

None of the cases was studied in the presence of a complicating illness, such as bronchopneumonia. All were examined at sea level and none had lived for any length of time at a high altitude.

RESULTS

I Uncomplicated pulmonary insufficiency (Groups 1, 2 and 3)

A Clinical characteristics

The clinical histories of the patients belonging to Groups 1, 2 and 3, with pulmonary insufficiency, are essentially similar. The duration of the common symptoms of repeated respiratory infections, associated with chronic cough and progressive exertional dyspnea tends to lengthen as one progresses from Group 1 to Group 3. The incidence of asthma, pleurisy and serious pulmonary infection in the past history does not vary from group to group. Nine cases with silicosis are included. The physical examination did not demonstrate any significant variation among the groups. In most cases the thorax was distended and held in the inspiratory position. Thoracic expansion usually was limited, with absence of the lateral flare. Frequently respiration was either upper costal in type or else the thoracic cage was moved upward as a unit, by action of the accessory muscles of respiration. Uncoordinated respiratory movements were common. Breath sounds were diminished, rhonchi and sibilant rales were present as a rule. The heart was small in all cases. Clubbing of the fingers was observed in about one-third of the patients. None was polycythemic. The chest x-rays showed hyperaeration of the lung fields in variable combination with increased bronchovascular markings or definite pulmonary fibrosis. The diaphragmatic contour became lower, flatter and more irregular progressively from the first to the third group. The majority of the electrocardiograms in the standard leads were normal, with variable axis deviation.

The pulmonary arterial pressures of twenty patients belonging to Groups 1, 2 and 3 were measured at rest by means of the technique of right heart catheterization. Normal systolic pressures below 30 millimeters of mercury were found in nine cases, all with a normal arterial blood oxygen saturation at rest. (More recent studies have shown in similar cases an appreciable rise of the pulmonary arterial pressure during moderate exercise.) The systolic pressures of the remaining eleven cases were abnormally elevated, ranging from 30-50 millimeters of mercury, all but one presenting arterial anoxia at the time of the study. In general, the blood volumes were normal or low. Although these observations indicate the presence of physiological changes in the pulmonary circulation of such patients, we do not have sufficient data to establish these findings conclusively.

None of the cases belonging to Groups 1, 2 and 3 progressed to Group 4 by developing chronic congestive heart failure while under observation. However, acute episodes of cardiac failure were precipitated not infrequently in these patients by acute anoxia resulting from a sudden decrease of pulmonary reserve due to the development of pneumonia or the induction of a pneumothorax (13). Although such episodes may be terminal, as in one of the cases belonging to

Group 2, the patient may also rapidly return to his previous state without sequelae. The majority of our patients were sent to the hospital only for evaluation and were subsequently followed by their private physicians. Follow-up data over periods of one to thirteen years are, however, available on thirty-one cases. Of these, ten were studied several times and ten are known to be dead. The causes of death of eight of these cases were as follows:

In Group 1, Fibrocaceous tuberculosis 2 cases, and status asthmaticus 1 case.

In Groups 2 and 3, Syndrome of pulmonary insufficiency, characterized by extreme dyspnea and anoxia, not relieved by oxygen breathing 4 cases, and bronchopneumonia complicated by acute cardiac failure 1 case.

B Physiological observations

The statistical data concerning the physical characteristics and physiological measurements of the fifty-nine patients completely studied with respect to their arterial blood gases will be found in tables 1 to 5. The most important data are illustrated in figures 7 to 10. The physiological characteristics of each of the three groups will be described in turn.

Group 1 In this group of twenty-five cases with an arterial oxygen saturation of 92 per cent or more following the standard exercise test the physiological findings were as follows:

1 The mean total capacity was slightly greater than the predicted value and the mean vital capacity was 72% of the predicted value. The mean residual air/total capacity ratio $\left(\frac{R}{T} \frac{A}{C} \times 100 \right)$ was considerably elevated, up to 48.

2 The mean maximum breathing capacity was reduced to 43 per cent of the predicted value. It was more than 50 per cent of the predicted value in only seven cases. Following the use of a bronchodilator spray, the mean maximum breathing capacity increased by 11 per cent.

3 The majority of the spiograms showed considerable slowing of expiration which is characteristic of bronchiolar obstruction, loss of alveolar elasticity, and trapping of air. The maximum breathing capacity was performed in a high inspiratory position, usually the volume of each individual breath during this test was less than 30 per cent of the vital capacity and sometimes smaller than the tidal air volume during quiet breathing.

4 A small degree of hyperventilation or a high normal ventilation was present during all the periods of observation. The mean breathing reserves during the standard exercise test and the first minute of recovery were respectively 21 and 16 liters, sharply below estimated normal values. The mean breathing reserve during the last minute of dyspnea following the standard exercise test was 44 per cent of the maximum breathing capacity and 56 per cent during the first minute without dyspnea.

5 The mean index of intrapulmonary mixing equal to 55 per cent was abnormally high, indicating poor intrapulmonary distribution and mixing.

6 The mean oxygen consumption was essentially normal at rest, during exercise and during the first five minutes of the recovery period.

TABLE 1
Physical Characteristics in Sixty Eight Patients with Chronic Pulmonary Emphysema

	GROUP I				GROUP II				GROUP III				GROUP IV				
	No	Mean	S D	Range		Mean	S D	Range	No	Mean	S D	Range	No	Mean	S D	Range	
Male																	
Age in years	19	54	10	27-64		14	52	5	45-60	13	56	8	43-67	9	52	8	41-64
Weight in kilograms	19	61	11	40-81		14	65	10	40-88	13	60	12	44-74	9	61	12	43-78
Height in centimeters	19	168	7	157-181		14	173	9	156-192	13	171	8	160-179	9	167	10	156-175
Body surface area in m ²	19	1.71	0.16	1.47-1.92		14	1.76	0.17	1.48-2.16	13	1.69	0.17	1.42-2.09	9	1.69	0.16	1.51-1.83
Female																	
Age in years	6	36		17-60		5	38		23-62	2			14-63				
Weight in kilograms	6	51		45-59		5	45		39-51	2			38-70				
Height in centimeters	6	155		145-165		5	158		157-163	2			161-169				
Body surface in m ²	6	1.48		1.36-1.65		5	1.41		1.37-1.53	2			1.26-1.90				

TABLE 2
Lung Volumes and Maximum Breathing Capacity in Sixty Eight Cases with Chronic Pulmonary Emphysema

	GROUP I			GROUP II			GROUP III			GROUP IV		
	No	Mean	S.D.	Range	No	Mean	S.D.	Range	No	Mean	S.D.	Range
Lung volumes in per cent of predicted value												
Vital capacity	25	72	16	47-105	19	69	19	42-100	15	59	11	45-78
Residual air	25	199	65	102-332	19	181	53	102-289	15	203	53	120-306
Total capacity	25	105	18	71-137	19	99	21	65-142	15	99	17	72-149
Residual air Total capacity $\times 100$	25	48	8	30-69	19	60	9	36-63	15	58	6	49-69
Maximum breathing capacity per cent of predicted value												
Before bronchodilator	25	43	16	21-82	19	37	14	15-63	15	29	7	17-42
After bronchodilator	23	51	16	27-94	19	45	14	19-73	15	36	7	27-48

TABLE 3
*Ventilation and Breathing Reserve during the Standard Exercise Test and Index of Intra-Pulmonary
 Mixing in Sixty-Eight Cases with Chronic Pulmonary Emphysema*

	GROUP I					GROUP II					GROUP III					GROUP IV				
	No	Mean	S D	Range	No	Mean	S D	Range	No	Mean	S D	Range	No	Mean	S D	Range	No	Mean	S D	Range
Ventilation in L/min/m ² B S																				
Basal	25	4.7	0.9	2.9-6.0	19	4.8	3.2	3.3-5.7	15	4.3	0.7	3.0-5.5	9	3.9	0.6	3.3-4.3				
1 min standard exercise	25	12.6	2.5	8.6-17.7	19	12.6	3.2	5.4-17.8	15	10.7	1.8	8.5-14.5	9	8.5	1.1	6.7-10.6				
1st min recovery	23	13.9	2.8	9.1-23.0	19	14.6	3.3	6.4-20.7	15	12.2	1.2	10.0-14.2	9	11.1	2.5	7.1-15.7				
5th min recovery	24	7.8	2.6	4.0-16.3	17	7.4	1.3	5.0-10.2	14	7.4	1.0	5.5-9.1	9	6.5	1.6	4.3-9.1				
Breathing Reserve																				
Max Breathing Capacity $\times 100$																				
Last min. with dyspnea	21	44	16	11.0-60	15	25	15	0-50	8	19	7.0	10-30	5	36		5-59				
First min. without dyspnea	20	56	25	3.0-75	15	41	12	15-59	8	34	6.0	22-42	5	49		21-73				
Breathing reserve in liters																				
1 min standard exercise	24	21	16	0-58	19	12	8	0-29	15	10	5	0-19	9	16	10	5-42				
1st min recovery	22	18	12	0-48	18	7	3	0-24	15	6	5	0-15	9	14	10	0-41				
Index of intra-pulmonary mixing																				
Alveolar N ₂ per cent after 7 min pure O ₂ breathing	22	5.5	2.8	2.6-11.3	19	6.8	2.9	2.5-12.8	14	6.9	2.8	3.4-14.3	9	7.1	1.7	3.4-9.0				

TABLE 4

Oxygen Consumption during the Standard Exercise Test in Sixty eight Cases with Chronic Pulmonary Emphysema

	GROUP I				GROUP II				GROUP III				GROUP IV			
	No	Mean	SD	Range	No	Mean	SD	Range	No	Mean	SD	Range	No	Mean	SD	Range
Oxygen Consumption in cc/min/m ² B.S.																
Basal	25	137	12	114-186	19	147	20	120-194	15	143	13	120-172	9	145	15	129-172
1 min standard exercise	25	455	102	291-700	10	413	138	153-730	15	404	80	319-499	9	304	53	238-376
5 min recovery period	15	1435	181	1150-1900	11	1475	231	990-1851	13	1663	131	1450-1820	9	1630	108	1350-1871
Oxygen intake in cc/Lit of ventilation																
Basal	25	36.3	7.8	21.8-54.4	19	35.0	3.8	28.0-42.1	15	39.0	5.4	33.3-51.7	9	42.5	7.8	36.0-51.6
1 min standard exercise	25	41.8	7.6	26.8-61.8	19	37.0	5.9	25.8-47.4	15	42.4	0.2	29.1-55.0	9	41.0	5.9	34.6-47.8

TABLE 5

Respiratory Gases in the Arterial Blood during Rest and following the Standard Exercise Test of Sixty eight Cases with Chronic Pulmonary Emphysema

	GROUP I				GROUP II				GROUP III				GROUP IV			
	No	Mean	SD	Range	No	Mean	SD	Range	No	Mean	SD	Range	No	Mean	SD	Range
Oxyhemoglobin saturation in per cent																
Basal	24	95.0	3.0	89.4-98.0	19	89.5	4.0	70.0-98.0	15	89.4	2.8	85.6-93.0	9	82.0	9.7	65.4-91.0
1st min recovery	25	94.8	1.8	92.0-98.0	19	82.2	9.4	57.0-90.8	15	78.6	8.0	58.3-89.3	9	75.8	10.0	65.8-88.0
Carbon dioxide content in vols %																
Basal	24	49.0	4.3	43.0-59.2	19	50.6	3.6	41.0-55.4	15	55.8	4.1	49.1-63.0	9	62.2	3.0	50.0-67.0
1st min recovery	25	47.3	4.4	40.8-61.8	19	48.2	2.9	40.0-53.0	15	56.2	4.6	51.6-61.6	9	61.1	2.0	53.8-65.0
Carbon dioxide tension in mm Hg																
Basal	24	39.6	5.4	31.4-50.1	19	39.7	3.0	31.0-45.2	15	47.9	4.3	38.0-57.0	9	58.7	7.1	51.0-70.0
1st min recovery	25	40.4	4.4	35.2-55.6	19	41.1	3.9	33.8-48.8	15	52.2	4.5	48.0-63.0	9	62.4	9.0	55.4-80.0
Carbon dioxide content at 40 mm Hg (T ₄₀) in vols %																
Basal	25	49.5	2.2	45.7-54.6	19	51.0	3.1	43.3-54.8	14	51.0	3.7	45.4-57.5	9	53.5	2.7	47.0-57.5
1st min recovery	24	47.0	7.7	41.0-52.1	19	47.6	3.0	41.3-53.0	14	49.3	3.5	43.3-54.4	9	50.5	4.5	45.1-57.0
pHs																
Basal	24	7.43	0.02	7.39-7.45	19	7.41	0.03	7.38-7.45	15	7.41	0.03	7.33-7.45	9	7.35	0.05	7.29-7.39
1st min recovery	25	7.41	0.03	7.33-7.45	19	7.41	0.03	7.35-7.45	15	7.38	0.04	7.29-7.42	9	7.32	0.05	7.25-7.39

7 The mean arterial oxygen saturation at rest and following exercise was normal. It should be noted that in six cases the arterial blood oxygen saturation

was between 88 and 92 per cent at rest and rose to normal values following exercise

8. The mean arterial carbon dioxide tensions, alkaline reserve (T_{40}) and pHs were normal both at rest and following exercise

Comment It is apparent from these results that this group suffers predominantly from severe ventilatory insufficiency. The sharp reduction in breathing reserve is caused mainly by a large restriction in the maximum breathing capacity. Hyperventilation is present, although minimal, and compensates adequately for the disturbance in respiratory gas distribution, as shown by the relatively normal state of the respiratory gases in the arterial blood, especially after exercise

Group 2 In this group of nineteen cases with an arterial oxygen saturation below 92 per cent and a carbon dioxide tension below 48 millimeters of mercury, following the standard exercise test, the physiological findings were as follows

1 The mean total capacity was about that predicted for the group, and the mean residual air was 50 per cent of the mean total capacity

2 The mean maximum breathing capacity was reduced to 37 per cent of the predicted value and was increased by 8 per cent following the use of a bronchodilator spray

3 The pattern of the spiograms was similar to that observed in the previous group

4 The mean ventilation during the periods of observation was increased to about the same extent as in the previous group. The mean breathing reserves during the standard exercise test and the first minute of recovery were respectively 12 and 7 liters, values considerably lower than those of the previous group. The mean breathing reserve during the last minute of dyspnea following the standard exercise test was 25 per cent of the maximum breathing capacity, rising to 41 per cent during the first minute without dyspnea.

5 The mean index of intrapulmonary mixing, equal to 6.8 per cent, was definitely higher than that of the previous group, although, because of the wide scatter of the individual values, the difference has no statistical significance

6 The mean oxygen consumption, while slightly reduced during exercise, remained within normal limits at rest and during the first five minutes of the recovery period

7 Arterial anoxia was present at rest in the majority of the cases and increased greatly following exercise

8 The mean arterial carbon dioxide tension, alkaline reserve (T_{40}) and pHs were normal at rest as well as following exercise

Comment From these results it is evident that this second group differs markedly from the first on account of a greater degree of ventilatory insufficiency and because of the presence of arterial anoxia. There is little, if any, difference between the two groups with respect to the size and distribution of the lung volumes.

In view of the markedly unequal distribution of the tidal air, the arterial anoxia is probably due, at least in part, to a poor correlation between alveolar

ventilation and perfusion, with persistence of blood circulation in poorly ventilated alveoli. It is possible also that inadequate diffusion plays a part, due to diminished alveolar capillary surface or to thickened alveolar walls, these factors cannot be isolated or evaluated in these cases by the methods used. As has been pointed out by others in the past, unequal distribution of tidal air, with arterial anoxia, is compatible with normal arterial carbon dioxide tensions and pHs, since over-ventilated alveoli can eliminate more CO_2 , without increasing the oxygen uptake appreciably above normal saturation. The reduction in oxygen consumption during the exercise test of short duration is mainly due to the oxygen deficit caused by the arterial anoxia. The very severe restriction of the maximum breathing capacity greatly limits the breathing reserve.

Many cases belonging to this group differ from those in the previous group in only one respect, namely, the presence of arterial anoxia during exercise. The pulmonary function pattern of still other cases more closely resembles that of the following group. A certain overlapping must be expected because of the fixed criteria used to separate the three groups of cases.

Group 3 In this group of fifteen cases with an arterial oxygen saturation below 92 per cent and a carbon dioxide tension above 48 millimeters of mercury following the standard exercise test, the physiological findings were as follows:

1 The mean total capacity, as in the previous two groups, was close to the predicted value, the mean residual air/total capacity ratio $\left(\frac{R.A.}{T.C.} \times 100\right)$ was 58, a value significantly greater than the mean values for either Group 1 or 2 (Respectively $P = .003$ and $P < .0004$).

2 The mean maximum breathing capacity was restricted to 29 per cent of the predicted value. The difference between the mean value of this group and Group 1 has statistical significance ($P < .0004$). The differences between the means of Groups 2 and 3 are not significant. In only nine cases was the maximum breathing capacity improved by the use of a bronchodilator spray.

3 The spirogram showed the pattern of marked bronchiolar obstruction and air trapping. The maximum breathing capacity in most cases was performed in an extreme inspiratory position, which was higher than that attained during a single maximum inspiration.

4 In sharp contrast to the previous two groups, the ventilation during the minute of exercise and the first minute of recovery was not increased above the mean normal values in any case and was lower than normal in most of them. However, at rest and during the fifth minute of recovery it was increased to the same extent as observed in the preceding groups. The mean breathing reserves during the standard exercise test and the first minute of recovery were respectively 10 and 6 liters. The mean breathing reserve during the last minute of dyspnea was 19 per cent of the maximum breathing capacity, rising to 34 per cent during the first minute without dyspnea. Seven of the fifteen cases were dyspneic for more than five minutes.

5 The mean index of intrapulmonary mixing did not differ significantly from the similar value in Group 2, the range was approximately the same.

6 The mean oxygen consumption during rest was the same as in the previous groups. The mean oxygen consumption during exercise was somewhat lower than in the previous groups. Statistically this figure is significantly lower than that observed in the normal control groups ($P < .003$). The mean oxygen consumption during the five minute recovery period is considerably greater than that found in either the control or the two other emphysematous groups, although the wide scatter prevents this difference from having statistical significance.

7 The mean arterial oxygen saturation during rest was identical to that found in Group 2, but fell to a considerably lower value following exercise.

8 The mean arterial carbon dioxide tension was abnormally high at rest as well as following exercise. There was a definite tendency for respiratory acidosis to develop after exercise.

Comment. From these results it would appear that the degree of emphysema in this third group is more severe than in the two preceding groups, and that extreme ventilatory as well as alveolar respiratory insufficiency is present. The reduction of the breathing reserve to almost vanishing values during exercise and the first minute of recovery is in sharp contrast to the considerable degree of hyperventilation observed during rest and the fifth minute of recovery. This would seem to indicate that the absence of hyperventilation observed during exercise and the first minute of recovery is due to mechanical limitation of the ventilation and not to a depression of the respiratory centers. These data suggest that the deterioration of the alveolar respiratory function is in part the result of ventilatory failure. The requirement of the standard exercise test can no longer be met by an adequate increase in ventilatory effort and the alveolar ventilation is considerably reduced. This situation results in retention of carbon dioxide as well as in severe arterial anoxia. It is probable, however, that the disturbance of air distribution also has progressed in comparison with the preceding groups. It is impossible to judge from the available data whether or not an impairment of diffusion of oxygen across the alveolo-capillary membrane plays a role in the alveolar respiratory insufficiency. Other methods, not available at the time of these studies, are required for the solution of this problem. Whether or not the reduction in O_2 intake during the period of exercise is due only to the decrease in arterial oxygen saturation, without the additional factor of a smaller than normal increase in cardiac output, cannot be decided.

C Individual case studies

The following seven cases have been selected to illustrate further the pulmonary pattern characteristic of each group and to show the influence of the progression of the disease upon these patterns in patients studied repeatedly over a period of years.

Case 1. This case shows the findings typical of Group 1. C. S., a 59 year old white male with a body surface area = 2.04 m^2 , entered the clinic complaining of extreme breathlessness, cough and sputum for the past nine years. For a period of at least eighteen years he had suffered from recurrent heavy chest colds often associated with fever. On physical examination the chest was distended, with relatively good motion. There was marked hyperresonance and the breath sounds were emphysematous with many sibilant rales and

rhonchi. The heart was small, the sounds distant. X ray examination of the chest showed marked hyperaeration of the lung fields with some increase of the broncho vascular markings. The costophrenic sulci were blunted and the diaphragms were low but not flattened.

TABLE 6

Physiological Measurements in 3 Individual Cases of Chronic Pulmonary Emphysema Showing the Characteristic Findings of Groups 1, 2 and 3

	CASE 1		CASE 2		CASE 3	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1 Lung volumes in cc						
Vital capacity	3142	3850	4720	4290	2980	3800
Residual air	3748	1720	2828	1300	5175	1690
Total capacity	6890	5570	7098	5590	8155	5490
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	55	31	40	31	63	31
2 A Maximum breathing capacity in L/min						
Before bronchodilator	40	113	63	132	31	109
After bronchodilator	62		86		34	
B Ventilation in L/min/m ²						
BS						
Basal	4.3	3.9	4.7	3.9	5.5	3.9
1 min standard exercise	11.6	11.2	15.9	11.2	9.9	11.2
1st min recovery	18.8	14.5	16.0	14.5	12.3	14.5
C Breathing reserve in liters						
1 min standard exercise	16	90	29	108	11	86
1st min recovery	2	83	29	101	6	79
3 A Index of intra pulmonary mixing alveolar N ₂ %	7.7	<2.5	5.9	<2.5	14.3	<2.5
B Arterial blood						
Oxyhemoglobin saturation %						
Basal	89	96	90	96	85.8	96.0
1st min recovery	96	96	84	96	64.8	96.0
Carbon dioxide tension in mm Hg						
Basal	38	43.7	36.1	43.7	50.0	43.7
1st min recovery	40.8	43.0	35.0	43.0	52.4	43.0
4 Oxygen consumption in cc/min/m ²						
BS						
Basal	125	132	138	132	172	132
1 min standard exercise	440	506	503	506	382	506

The heart shadow was small. On fluoroscopic examination diaphragmatic motion, although extremely slow, was abnormally small in amplitude. The patient's symptoms are somewhat relieved at present by bronchodilator drugs.

The physiological data (table 6) revealed

1 a marked increase of the total lung volume,

- 2 a moderate increase of the residual air/total capacity ratio $\left(\frac{R A}{T C} \times 100\right)$,
- 3 a restricted maximum breathing capacity with great improvement following the use of a bronchodilator spray,
- 4 hyperventilation at rest and during the recovery period,
- 5 a large increase in the index of intrapulmonary mixing and
- 6 slight arterial anoxia at rest which disappeared following exercise

During right heart catheterization studies, the pulmonary arterial pressures were found to be normal

The pulmonary pattern is characterized by marked restriction in the ventilatory capacity associated with disturbance of the distribution of the tidal air. The latter is compensated by hyperventilation, especially as a result of increased physical activity so as to maintain a normal alveolar ventilation. The major disability of the patient, therefore, is severe ventilatory insufficiency

Case 2 This case shows the findings typical of Group 2. F. D., a 48 year old male with a body surface area = 2.16 m², complained of progressive exertional dyspnea of one year's duration, associated with wheezing. There was no orthopnea or history of frequent upper respiratory infection. On physical examination no cyanosis was apparent, the chest was distended with limited respiratory movements and the breath sounds were distant with prolonged expiration. Fluoroscopic examination revealed marked hyperaeration of the lung fields and a small heart. The diaphragmatic motion was only slightly impaired. The patient was not followed.

The physiological findings (table 6) differ from the previous case in only one respect, namely, the development of arterial anoxia following the standard exercise test.

Hyperventilation during all the periods of observation compensates for the disturbance in distribution by maintaining a more than adequate overall alveolar ventilation. This is attested by the reduction of the arterial carbon dioxide tension. The arterial anoxia, following the standard exercise test, on the other hand, must be the result of either an increased alveolar capillary oxygen diffusion gradient, or else the perfusion of poorly, or non-ventilated alveolar spaces, in effect an intrapulmonary veno-arterial shunt. In this case, as in the previous one, a normal rise in oxygen consumption during the standard exercise test was an indication of a normal cardiac output response.

Case 3 This case shows the findings typical of Group 3. W. P., a 65 year old white male with a body surface area = 2.09 m², complained of increasingly severe exertional dyspnea and a chronic persistent cough, which had been present for many years. Four years previous to study he had developed a spontaneous pneumothorax. Patient had no orthopnea or cardiac symptoms, but had been treated as a cardiac with digitalis for several years. On physical examination slight cyanosis was apparent. The chest was distended with diminished respiratory movement. The breath sounds were distant with an occasional sibilant rale or expiratory rhonchus. The heart was not enlarged and the sounds were distant. Blood pressure 180/110. X-ray of the chest showed considerable hyperaeration with some bulla formation. The diaphragms were low in position and flattened. The cardiac shadow was small. The electrocardiogram showed slight evidence of myocardial damage. The patient at the present time is doing well on limited activity, the regular use of bronchodilator drugs and oxygen therapy by mask four or five times a day.

The physiological data (table 6) revealed

- 1 a large increase in total lung volume with
- 2 a large absolute and relative increase of the residual air,
- 3 a low maximum breathing capacity slightly improved by bronchodilator drugs,
- 4 a reduction in ventilation during the standard exercise test,
- 5 a large increase in the index of intrapulmonary mixing,

- 6 a marked arterial anoxia at rest, increasing greatly after exercise and associated with a high arterial carbon dioxide tension,
- 7 a low oxygen consumption during the minute of exercise

The degree of emphysema is considerably greater than in the previous cases. In spite of the reduced ventilation observed during the standard exercise test, the breathing reserve during the minute of exercise and the first minute of recovery is lower than in the two preceding cases. With this limitation of the overall ventilation no compensation is possible for the disturbance in the distribution of tidal air. However, at rest, even in the presence of hyperventilation the alveolar ventilation is grossly inadequate as reflected in a high arterial carbon dioxide tension. The data at hand cannot help to determine whether impairment of diffusion also plays a part in the severe arterial anoxia. With a marked reduction in arterial oxygen saturation, the low oxygen consumption during exercise could be the result of either the alveolar respiratory insufficiency or an inadequate cardiac output response. In summary, this case, in addition to an extreme degree of ventilatory insufficiency also suffers from severe alveolar respiratory insufficiency.

Case 4 This case was studied twice over a three year period. In the first study slight evidence of pulmonary dysfunction was present, while in the second the findings were typical of Group 2. E. S., a 45 year old white male with a body surface area = 1.90 m², was first seen in 1944 with the single complaint of exertional dyspnea. His respiratory and cardiac history was otherwise completely unrevealing. At this time his physical examination was essentially negative, except for the moderately emphysematous contour of his chest. Three years later he returned for reexamination without any striking change in his symptomatology. There had been no intermittent respiratory infections or attacks of bronchial spasm. The chest x-rays on both occasions showed little other than moderate hyperinflation of the lung fields. The patient recently moved and therefore has not been followed.

The physiological findings (table 7) during the first examination revealed a small increase in total lung volume mostly due to an increase in residual air, a slightly elevated residual air/total capacity ratio ($\frac{R}{T} \times 100$), some reduction of the maximum breathing capacity and a slight reduction in the arterial oxygen saturation, with a return to normal following the standard exercise test, as a result of a considerable increase in ventilation and a more than adequate alveolar ventilation.

Three years later the studies showed a further increase in residual air, a greater reduction in maximum breathing capacity, a high index of intrapulmonary mixing, and an arterial anoxia present both at rest and following exercise, with evidence of adequate alveolar ventilation as judged from the carbon dioxide tensions.

The case is of particular interest because of the minimal findings at the time of the first study. The patient was considered then to be suffering from a respiratory neurosis. The abnormal findings in the study made three years later were a complete surprise in view of the fact that the patient's symptoms had not increased. It should be noted that the maximum breathing capacity of this case was not restricted to the same extent as those of the previous cases and therefore the breathing reserve during the standard exercise test was relatively large. This may well account for the mild symptoms.

Case 5 This case was studied twice over a period of ten years and illustrates the progression from severe ventilatory insufficiency to combined ventilatory-alveolar respiratory insufficiency. I. H., a 37 year old Negro with a body surface area = 1.43 m², was first seen in 1935 complaining of cough and mild exertional dyspnea of one year's duration. He had worked as a rock driller and blaster for two years and had been told that he had silicosis. On physical examination there was no cyanosis. Chest expansion was diminished over the lower lobes, although both diaphragms descended well. The lower chest was pulled in during inspiration. Breath sounds were diminished and associated with sibilant rales

and rhonchi The heart borders could not be percussed but the sounds were of good quality although distant A2 > P2 Blood pressure was 195/100 X-ray of the chest showed moderate accentuation of the bronchovascular shadows throughout both lung fields but no nodulation The heart was slightly increased in the transverse diameter and the as-

TABLE 7
Physiological Measurements in 2 Individual Cases of Chronic Pulmonary Emphysema Studied Twice Over a Period of Years

	CASE 4			CASE 5		
	1944	1947	Predicted	1940	1948	Predicted
1 Lung volumes in cc						
Vital capacity	4056	3875	3900	2652	1953	3800
Residual air	1874	2275	1145	2130	3467	1230
Total capacity	5930	6150	5045	4782	5420	5030
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	32	39	23	46	64	23
2 A Maximum breathing capacity in L/min						
Before bronchodilator	87	74	119	27	16	102
After bronchodilator	90	103		42		
B Ventilation in L/min/m ² B S						
Basal	3.9	3.8	3.9	5.0	8.4	3.1
1 min standard exercise	18.0	12.0	11.2	12.7		10.0
1st min recovery	19.6	14.3	14.5			
C Breathing reserve in liters						
1 min standard exercise	58	52	98	7		86
1st min recovery	55	48	92			
3 A Index of intra-pulmonary mixing alveolar N ₂ %	1.7	9.5	<2.5	3.9	12.5	<2.5
B Arterial blood						
Oxyhemoglobin saturation %						
Basal	92	90	96	92	95	96
1st min recovery	96	89	96	95	89	96
Carbon dioxide tension in mm Hg						
Basal	35.0	37.0	43.7		51.0	43.7
1st min recovery	31.5	39.0	43.0			
4 Oxygen consumption in cc/min/m ² B S						
Basal	133	127	132			
1 min standard exercise	556	387	506			

ending aorta was widened and tortuous Electrocardiogram showed slight evidence of myocardial damage During the next five years the patient's condition remained stationary The dyspnea and cough were improved by bronchodilator drugs The hypertension did not progress In 1944 the patient stopped work because of dyspnea At this time his physical examination was essentially unchanged There was no evidence of cardiovascular failure During the following four years dyspnea increased markedly until the last

admission when the patient was practically confined to his bed. There was no clinical evidence of cardiac insufficiency, in spite of his severe long standing pulmonary insufficiency and systemic hypertension. X-ray of the chest at this time showed marked uniform hyperaeration of both lung fields with flattening of the diaphragms. The heart was not enlarged, although there was a sacular aneurysm of the ascending aorta. The patient was transferred to another institution for custodial care.

Incomplete pulmonary function studies were performed in 1940 and 1948 and are presented in table 7. The findings in 1940 show the pattern typical of Group 1, characterized

by a considerable increase of the residual air/total capacity ratio $\left(\frac{R A}{T C} \times 100\right)$, a marked

restriction of the maximum breathing capacity greatly improved by bronchodilator drugs (restriction of the same degree had been observed in 1935) and a normal arterial oxygen saturation following exercise. In 1948 the studies revealed a great increase of the residual

air/total capacity ratio $\left(\frac{R A}{T C} \times 100\right)$, further reduction of the maximum breathing capacity and an extreme degree of hyperventilation at rest.

The arterial blood was still normally saturated with oxygen at rest but became unsaturated after the four or five steps' exercise that he was scarcely able to perform. On cardiac catheterization the resting pulmonary arterial pressures were found to be 38/16 millimeters of mercury.

Compared with the previous study the latest one shows a marked progression of the ventilatory insufficiency and the development of manifestations of alveolar respiratory insufficiency. The high resting arterial carbon dioxide tension suggests that alveolar ventilation is inadequate in spite of marked hyperventilation. With the least increase in activity all compensating mechanisms fail because of the extreme limitation of ventilatory capacity and as a result the arterial blood oxygen saturation decreases significantly.

Case 6 This case, studied on four occasions at one year intervals, illustrates the effect of bronchopneumonia and of varying degrees of bronchiolar obstruction of the asthmatic type upon pulmonary function. E. B. H., a 27 year old female school teacher with a body surface area = 1.44 m², suffered from chronic asthma since infancy. Acute attacks were aggravated by multiple allergies as well as by recurring respiratory infections, including frequent episodes described as bronchopneumonia. Exertional dyspnea and chronic cough had been present since childhood. The patient was followed in the clinic for six years, during which time she was hospitalized on one occasion for severe bronchopneumonia. No significant change was noted in the physical examination over the many years of observation. She was usually tachypneic, cyanotic and wheezing audibly. Her chest was distended and the accessory muscles of respiration were used to lift up the thoracic cage as a unit. Hyperresonance was marked, the diaphragms were low but mobile. The breath sounds were emphysematous and usually masked by frequent rhonchi and sibilant rales. The chest x-ray showed marked hyperaeration of the lung fields with flattened and low diaphragms. Both costophrenic angles were obliterated. The heart shadow was not enlarged but there was some dilatation of the pulmonary conus and arteries. On fluoroscopic examination the diaphragms moved well. The radio translucence of the upper lung fields, however, did not change during expiration. Repeated electrocardiograms have been normal. The patient does both teaching and housework and relies heavily upon bronchodilator drugs.

The physiological observations made at yearly intervals between 1943 and 1946 are presented in table 8. A progressive increase of emphysema may be noted throughout the years. The study of 1944 was made during a period of unusual good health and sense of well being. At this time no arterial anoxia was observed and the maximum breathing capacity showed considerable improvement. In contrast, the studies made in 1945, during convalescence from bronchopneumonia, show a sharp increase of the degree of emphysema

with considerable increase of the residual air/total capacity ratio $\left(\frac{R A}{T C} \times 100\right)$, a marked

TABLE 8

Physiological Measurements in 2 Individual Cases of Chronic Pulmonary Emphysema Studied Repeatedly Over a Period of Years

	CASE 6					CASE 7				
	1943	1944	1945	1946	Pre- dicted	1941	1942	1944	1945	Pre dicted
1 Lung volumes in cc										
Vital capacity	1974	2147	645	1244	3134	1936	2160	2140	2250	3820
Residual air	1550	2410	3100	2230	824	3760		3340	3400	1650
Total capacity	3524	4557	3745	3474	3950	5696		5480	5650	5600
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	44	53	83	64	21	66		61	60	31
2 A Maximum breathing capacity in L/min										
Before bronchodilator	19	37	10	19	84	16	25	19	17	90
After bronchodilator	35	49	28	30		22	35		28	
B Ventilation in L/min/m ²										
BS										
Basal	4 5	4 2		5 2	3 2	4 0	3 5	4 1	4 5	3 9
1 min standard exercise	9 4	9 5		9 2	9 0	6 8	8 1	5 4		11 9
1st min recovery	10 5	11 3		10 6	10 9	10 3	9 5	8 4		14 5
C Breathing reserve in liters										
1 min standard exercise	6	24		6	71	6	13	11		72
1st min recovery	4	21		4	68	0	11	6		68
3 A Index of intrapulmonary mixing alveolar N ₂ %	4 5	5 0	6 0	5 5	<2 5	16 7		14 4	13 8	<2 5
B Arterial blood Oxyhemoglobin saturation %										
Basal	95	93	87	86	96	93	90	95	94	96
1st min recovery	88	94		84	96	81	86	81		96

restriction of the maximum breathing capacity and arterial anoxia at rest as well as after exercise. By 1946 the extent of the emphysema had increased and the pulmonary pattern was quite characteristic of Group 3. In 1948 a moderate degree of pulmonary arterial hypertension was demonstrated by right heart catheterization.

The main interest in this case lies in the marked changes observed in the study of the pulmonary function during a period of relief from asthmatic attacks and during convalescence from a severe respiratory infection. In addition it shows the slow but definite progression of the functional disability over a period of 3 years.

Case 7 This case, classified in Group 3, was studied frequently during the four years preceding death. It illustrates a remarkable constancy of the physiological findings. H. C., a 50 year old white male with a body surface area = 1.52 m² was first admitted to the hospital in October, 1911 complaining of a chronic cough of twenty years' and of increasing dyspnea of five years' duration. On physical examination the patient was thin and pale with marked orthopnea, dyspnea and cyanosis; the upper chest appeared distended, the diaphragms were low and a dorsal kyphosis was present. Respiratory movements were of the upper costal type with an immobile box-like lower chest. Breath sounds were diminished. The heart was small, the sounds distant, A₂ > P₂. For several years the patient was subjectively much improved by rest periods, and by the regular use of bronchodilator spray and potassium iodide. During the last year of his life, however, he had repeated large hemoptyses from a left upper lobe bronchiectasis and usually raised large amounts of sputum. His pulmonary insufficiency progressed rapidly during this time and he died two months after his last admission with manifestation of extreme ventilatory insufficiency. At no time in his entire course was there any clinical manifestation of cardiovascular insufficiency. A ray of the chest (see fig. 1) showed marked hyperinflation of the lung fields with increased bronchovascular markings. The diaphragms were low and somewhat irregular. The costophrenic sulci were blunted. The heart was small with fullness of the pulmonary conus. Several electrocardiograms in the conventional leads were essentially normal.

Physiological studies (see table 8) showed on four occasions a marked increase of the residual air, evidence of obstructed expiration and of air trapping on the spiograms, restriction of the maximum breathing capacity with considerable improvement by bronchodilator (the maximum breathing capacity was repeatedly measured over the span of years and was found never to exceed the values listed in the table), an increased index of intra-pulmonary mixing, hypoventilation during the standard exercise test, and severe arterial anoxia following exercise. The mean right ventricular systolic pressure was found to be elevated to 37 millimeters of mercury two years before death.

The autopsy revealed extensive bullous emphysema, bronchiectasis, and purulent bronchitis. The major bronchi were thickened and contained large amounts of yellow gray gummy material. On microscopic examination the small bronchi (fig. 2) were frequently plugged with exudate. There was a tremendous distension of most of the alveoli. The alveolar spaces were frequently confluent with the remains of fragmented septa projecting into the lumen. The general pattern of the elastic tissue was greatly disturbed. The elastic fibers were often interrupted although occasionally condensed. The walls of the pulmonary vessels were thickened and their lumina narrowed. The heart was not weighed but appeared small. On microscopic section muscular hypertrophy of the right ventricle was apparent.

The close correlation between the anatomical and physiological observations in this case is quite evident. The marked dilatation of the alveolar air spaces is reflected in the increased residual air/total capacity ratio $\left(\frac{R}{T} \times 100 \right)$. The bronchial obstruction and disrupted elastic tissue structure of the lung explain the spiographic finding. It is, however, of great interest that no marked degree of right ventricular hypertrophy or dilatation was found at autopsy, in spite of the physiological evidence of right ventricular hyper-

tension two years before death and the autopsy findings of severe disruption of the pulmonary capillary bed and pulmonary arteriolar sclerosis

II Combined cardio-pulmonary insufficiency (Group 4)

A Clinical characteristics

The clinical features of the cases belonging to Group 4 differ from those found in the preceding groups by nature of their selection on the basis of clinical evidence of chronic cardio-circulatory failure, and of enlargement of the heart by

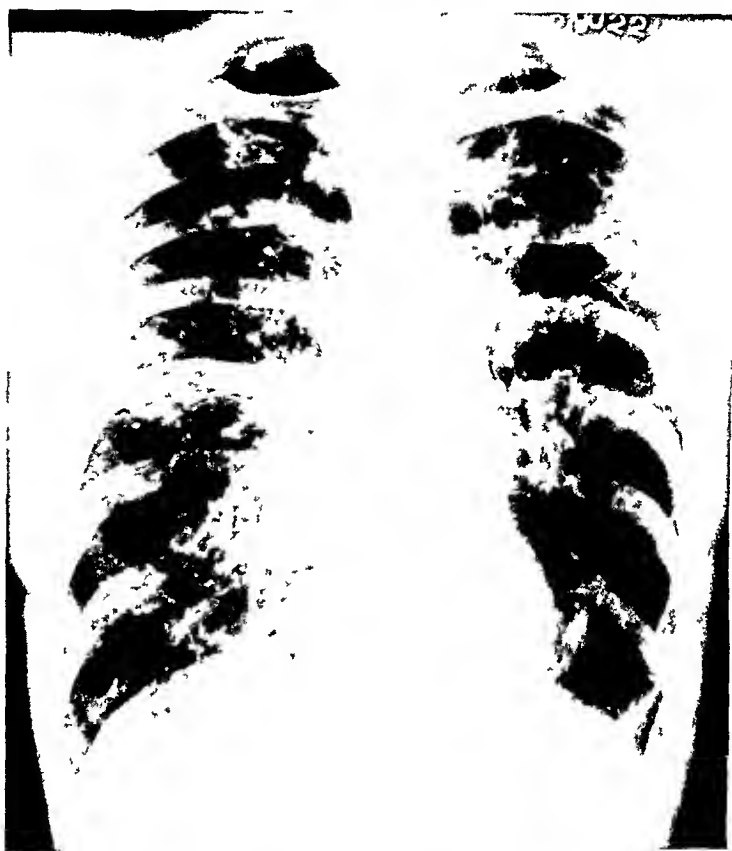


FIG 1 X-RAY PICTURE IN PATIENT H C (CASE 7) WITH ADVANCED PULMONARY EMPHYSEMA AND MARKED DEGREE OF ARTERIAL ANOXIA

x-ray All had congestive failure when first admitted to the hospital for evaluation. In addition to their pulmonary symptoms of chronic cough, repeated respiratory infections and exertional dyspnea, they complained in variable combinations of drowsiness, fatigue, weakness and dependent edema. On physical examination plethora, extreme cyanosis, dependent edema, ascites, enlargement of the heart and liver were often present in addition to the typical findings of chronic pulmonary emphysema described above. In all but one case polycythemia was present. In all cases the chest x-rays showed in addition to enlargement of the heart marked dilatation of the pulmonary arteries and fluoroscopic examination disclosed either paradoxical or greatly limited dia-

phragmatic movement. The electrocardiograms were abnormal in six patients with right axis deviation present as measured from conventional leads in seven of the nine records.

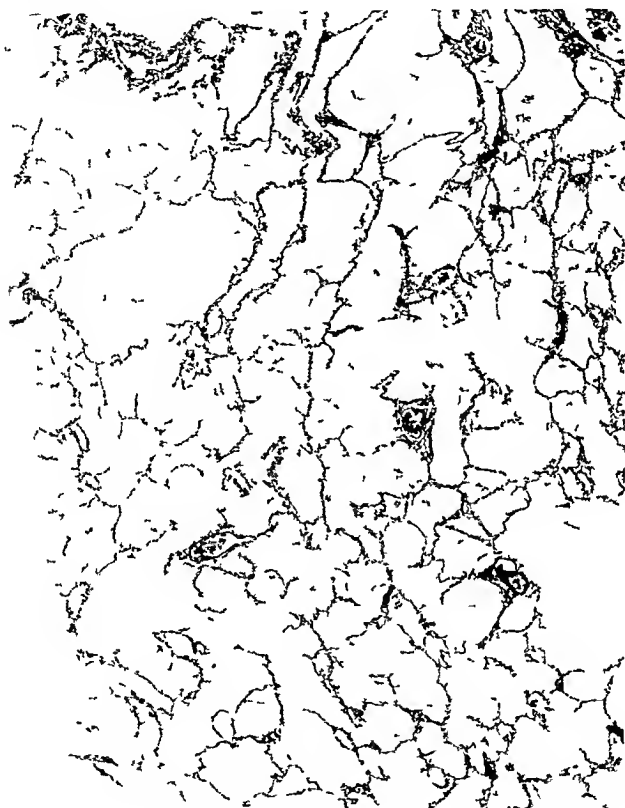


FIG. 2. MICROSCOPIC SECTION OF THE LUNG SHOWING THE CHARACTERISTIC HISTOLOGICAL FINDINGS IN PATIENT H. C. (CASE 7).

For description see text.

A total of nineteen patients belonging to Group 4 were partially or completely studied. Ten are known to have died from congestive heart failure within six weeks to nine years after their first study. Some of the patients ran a fairly rapid downhill course over a period of months, whereas others pursued a chronic course for many years. The cause of death was confirmed by autopsy in nine cases. In these cases the following diagnoses were made in addition to

that of chronic pulmonary emphysema and cor pulmonale chronic bronchiectasis and/or bronchitis in 5 cases, silicosis in 1 case and healed Boeck's sarcoid in 1 case

B Physiological observations

The statistical data concerning the physical characteristics and physiological measurements of the nine patients completely studied in respect to their arterial blood gases will be found in tables 1 to 5 and the most important data are illustrated in figures 7 to 10. The chief findings were as follows

1 The mean total capacity was slightly smaller than the predicted value. The mean residual air/total capacity ratio $\left(\frac{R A}{T C} \times 100\right)$ was approximately the same as that observed in Groups 1 and 2 of the uncomplicated pulmonary insufficiency series, and likewise significantly lower than in Group 3 ($P = .0004$)

2 The mean maximum breathing capacity was as low as in Group 3, but the range of variation was somewhat greater

3 The spiograms, in addition to the abnormalities observed in the preceding groups, showed more rounded curves, i.e. retardation appeared earlier in the expiratory phase

4 The mean ventilation during exercise and during the first minute of recovery was significantly lower than in Group 3. The statistical significance of the difference between the means during exercise is high ($P < .0004$). However, the difference during the first minute of recovery is less significant because of the small size of the two groups ($P = .01$). It is important to note that, in contrast to the observations made in the three previous groups, the mean ventilation at rest and during the fifth minute of recovery was normal. The mean breathing reserves during the standard exercise test and the first minute of recovery were respectively 16 and 14 liters, values considerably higher than in Groups 2 and 3. The mean breathing reserve during the last minute of dyspnea was 36 per cent of the maximum breathing capacity, rising to 49 per cent during the first minute without dyspnea. These values are more comparable with those found in Group 1 than with those in Groups 2 and 3.

5 The mean index of intrapulmonary mixing was almost identical with the values found in Groups 2 and 3.

6 The mean oxygen consumption during exercise was strikingly low. The differences between the values in this group and in the normal and preceding three groups have high statistical significance ($P < .0004$). The mean oxygen consumption during the five minute recovery period, on the other hand, was not different from the values obtained in Group 3.

7 The arterial oxygen unsaturation at rest and following exercise was of the same degree as in Group 3.

8 The mean carbon dioxide content and tension of the arterial blood during rest and following exercise were extremely high. The statistical differences between these mean values and similar values in group 3 are highly significant ($P = .005$ and $< .0004$ respectively). The pHs of the blood showed definite evidence of acidosis at rest and following exercise.

Comment From these studies it is evident that extreme ventilatory as well as alveolar respiratory insufficiency is present in this group. Whereas the degree of emphysema is about the same as in the two first groups, it is considerably less than that observed in Group 3. The cardio-circulatory insufficiency, however, is a significant additional factor. It is of interest that with an arterial oxygen unsaturation of the same degree as in Group 3 the oxygen consumption during exercise was greatly reduced in this group. This finding suggests that the cardiac output increase was less than in Group 3. Hypoventilation during exercise and recovery was striking and yet the breathing reserve during exercise and the first minute of recovery was higher than in Group 3. This finding suggests as a cause for the limitation of the ventilation a poor response of the respiratory center to the usually sharp stimulus of a high arterial carbon dioxide tension. Further depression of the ventilation shown by many of these cases when given high oxygen therapy is confirmatory evidence that their respiratory stimulus arises predominantly from the chemod body rather than from the medullary centers. The performance of these cases of cardio-circulatory failure associated with pulmonary insufficiency, contrasts sharply with that found in patients with uncomplicated congestive failure, during exercise, as in the latter group hyperventilation and a marked decrease in arterial carbon dioxide tension are usually observed.

As in the previous groups, the data do not permit an analysis of the respective parts played by disturbance of air distribution and impairment of diffusion in the production of the alveolar respiratory insufficiency.

C Individual cases

The following two cases have been selected to demonstrate that similar physiological patterns may be related to different pathological findings.

Case 8 This case was followed and repeatedly studied during the last nine years of his life. M. K., a Polish Jewish hat maker with a body surface area = 1.80 m², was first seen at the age of 38 years in April 1938, and was followed closely until his death in February, 1947. At the age of 28 years he developed a chronic productive cough with rapidly increasing exertional dyspnea which progressed during the next eight years to become his most disabling symptom. Cyanosis and ankle edema had been observed respectively for seven and six years. He had been treated in several hospitals, with only transient relief, for congestive failure and polycythemia by bed rest, phenylhydrazine, digitalis, phlebotomy and mercurial diuretics. When first seen in 1938 the patient was very cyanotic and wheezing audibly. The chest, held in the inspiratory position, was distended. Respiratory movements were limited and the accessory muscles of respiration moved the chest upwards as a unit. Breath sounds were diminished with numerous sibilant rales and rhonchi. The heart was large with a gallop rhythm, the liver was felt below the costal margin and moderate pretibial edema was present. Hemoglobin was 21.7 grms, red blood cells 8,460,000. There was a right preponderance and prolongation of the VV conduction time on the electrocardiogram. Chest x-ray (fig. 3) showed increased bronchovascular markings. The diaphragms were rounded and somewhat low in position. Marked cardiac hypertrophy was present with dilatation of the pulmonary arteries.

During the next nine years the physical examination and chest x-ray remained essentially unchanged although the disease slowly progressed. The pulmonary symptoms were greatly relieved by bronchodilator spray, which the patient insisted upon using continuously. Repeated phlebotomies were also beneficial. Drowsiness became extreme. Mas-

sive edema and ascites were difficult to control. The plasma volume ranged from 1980 to 2300 cubic centimeters per square meter body surface. The hematocrit was above 60. As a rule, cardiac rhythm was regular, but transient episodes of cardiac arrhythmia, auricular flutter and fibrillation were observed. Death occurred suddenly at home while the patient was alone.

Physiological studies were repeated during this long period of observation between 1938 and 1946. The data presented in table 9 are throughout the period of observation characteristic of Group 4. The following findings were strikingly constant, namely a total lung capacity always less than the predicted value, a considerable restriction of the maximum breathing capacity, with evidence of marked bronchiolar obstruction, until the

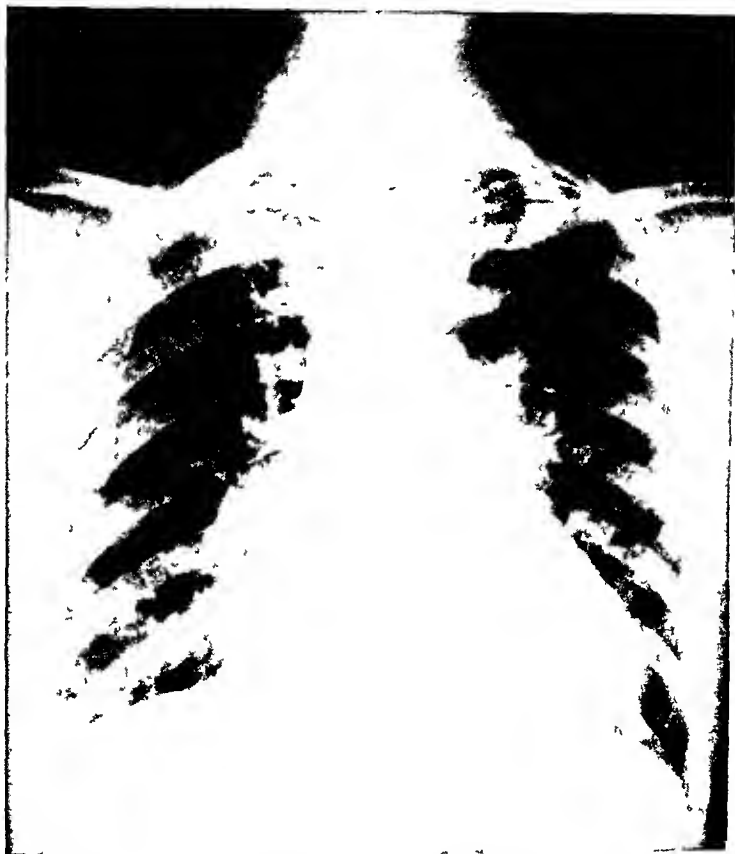


FIG 3 X-RAY PICTURE IN PATIENT M. K. (CASE 8) WITH MODERATE PULMONARY EMPHYSEMA, MARKED ARTERIAL ANOXIA, POLYCYTHEMIA AND CHRONIC CARDIAC FAILURE

last study the maximum breathing capacity doubled after the use of the bronchodilator spray, a marked hypoventilation in spite of a respiratory acidosis and a relatively large breathing reserve.

The progress of the disease was slow and is shown by a slowly progressive reduction of the maximum breathing capacity and of the arterial blood oxygen saturation.

Autopsy The lungs failed to collapse upon the opening of the thorax and a few bullae of 0.1-0.5 centimeter in diameter were seen subpleurally, the cut lung surface showed very little gross emphysema or distortion of lung structure except for lobar pneumonia in the left upper lobe. On microscopic examination (fig 4) the alveoli were for the most part uniform in size with moderate atrial dilatation. The alveolar walls were engorged with blood. Elastic tissue stains showed a minimal decrease in the number of elastic fibers in

the septa. The arterioles and precapillaries had as a rule normal walls, but a few of them showed thickening of the intima. There was no hypertrophy of the bronchiolar musculature although considerable fibrosis of the bronchiolar walls was seen. The heart was large, weighing 700 grams. The right auricle and ventricle were enormously dilated and hyper-

TABLE 9

Physiological Measurements in a Case of Chronic Pulmonary Emphysema with Cardio pulmonary Insufficiency, Studied Repeatedly Over a Period of 8 Years

	CASE 8						
	1938	1940	1942	1943	1945	1946	Pre dicted
1 Lung volumes in cc							
Vital capacity	2130	2230	2435	1650	1610	1680	4000
Residual air	1630	1684	2212	2085			1250
Total capacity	3760	3914	4647	3735			5340
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	43	43	48	56			24
2 A Maximum breathing capacity in L/min							
Before bronchodilator	24	30	31	9	14	11	115
After bronchodilator	46	53	46	10	26	23	
B Ventilation in L/min/m ² B S							
Basal	2.7	3.5	3.5				3.1
1 min standard exercise	5.4	7.4	6.6				10.0
1st min recovery			7.0				13.4
C Breathing reserve in liters							
1 min standard exercise	13	17	19				
1st min recovery			18				
3 A Index of intra pulmonary mixing, alveolar N %		13.4	13.2	7.4			<2.5
B Arterial blood							
Oxyhemoglobin saturation %							
Basal	76	79	65		61.0	57.0	96
1st min recovery	68	78	68				96
Carbon dioxide tension in mm Hg							
Basal	72.4		70.0		59.0	54.0	43.7
1st min recovery	75.0		80.0				43.0
4 Oxygen consumption in cc/min/m ² B S							
Basal	137	161	151				131
1 min standard exercise	290	322	268				181

trophied, whereas the left auricle and ventricle were approximately normal in size. The large pulmonary vessels were also tremendously dilated. A moderate number of atherosclerotic plaques were scattered over the intimal surface of the pulmonary arteries. No obvious obstruction to pulmonary blood flow was found. The liver and spleen showed chronic passive congestion.

These autopsy findings, in the light of the repeated physiological measurements, are of particular interest. They demonstrate very clearly that severe disturbances of the ventilatory and distributive functions of the lungs, associated with considerable distension of the lungs during life, are compatible with only moderate pathological evidence of emphysema and the persistence of the elastic structure of the lung. Bronchiolar obstruction of a

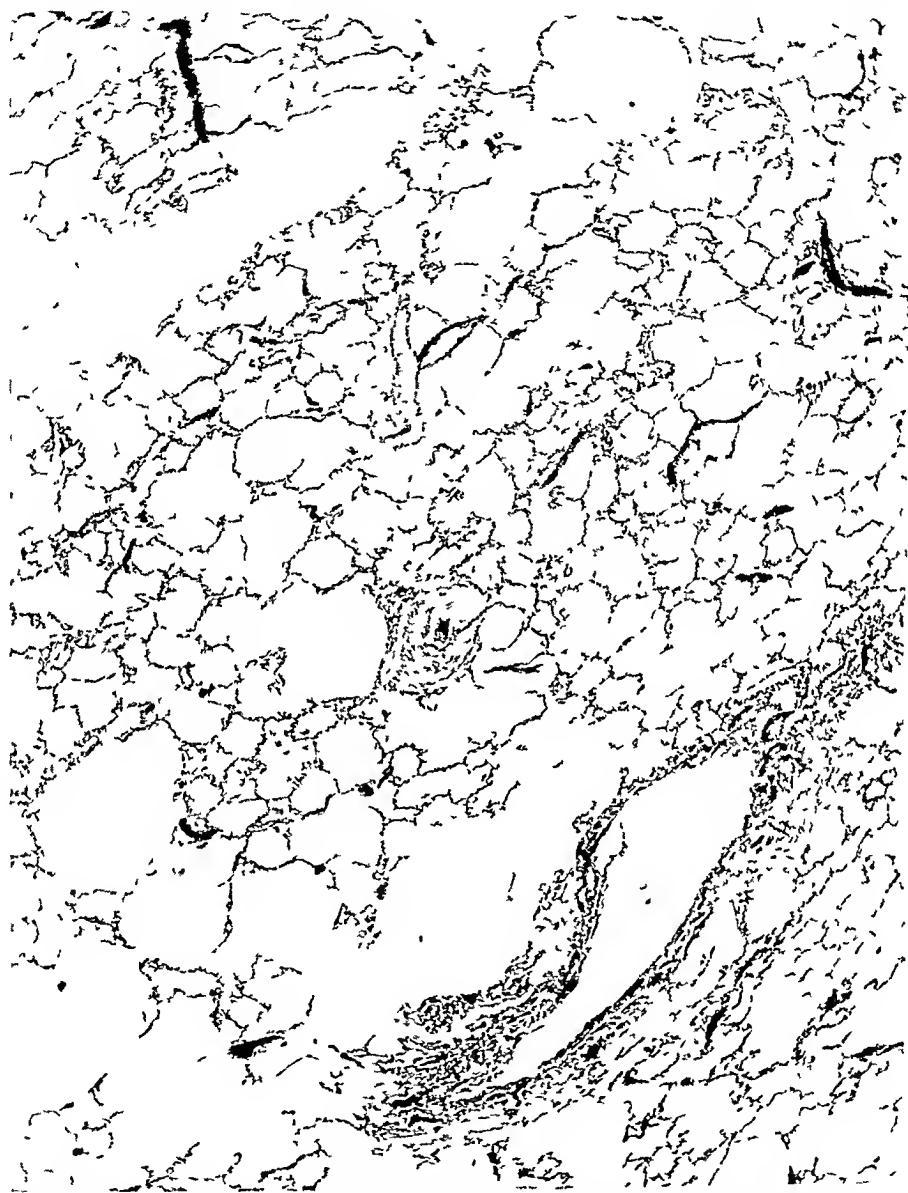


FIG 4 MICROSCOPIC SECTION OF THE LUNG SHOWING THE CHARACTERISTIC HISTOLOGICAL FINDINGS IN PATIENT M. K. (CASE 8)

For description see text

reversible type played an important part in the distension, with the additional factor of engorgement of the pulmonary vascular bed, a striking feature of the pathological findings. In this respect it is to be noted that a close correlation between the degree of ventilatory and distributive dysfunctions on the one hand, and the degree of polycythemia and plethora on the other, was frequently observed during the patient's lifetime. As for example, a marked subjective improvement, coupled with improvement in maximum breathing ca-

capacity and arterial saturation followed these episodes: 1) a severe hematemesis, 2) a bout of infectious jaundice, and 3) many large phlebotomies. Similarly, the great relief following the use of the bronchodilator spray could, in part, be the result of its vasoconstricting action on a congested bronchial wall, as bronchiolar muscular hypertrophy was strikingly absent. In an attempt to reconstruct the sequence of events which led to the clinical and physiological picture it may be postulated that, regardless of its nature, bronchiolar obstruction caused a disturbance in alveolar ventilation followed by a profound chronic anoxia, resulting in polycythemia and hypervolemia. Considerable increase in pulmo-

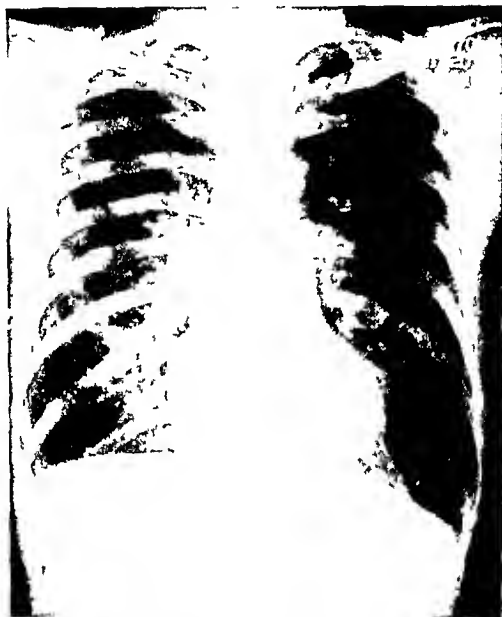


FIG. 5 X-RAY PICTURE IN PATIENT H. S. (CASE 9) WITH ADVANCED PULMONARY EMPHYSEMA, MARKED ARTERIAL ANOXIA, POLYCYTHEMIA AND PROGRESSIVE CARDIAC FAILURE.

nary blood volume and the increase in vascular resistance due to high viscosity of the blood may have played an important part in the development of right heart hypertrophy and dilatation to which pulmonary arteriosclerotic changes, or the shrinking of the pulmonary vascular bed contributed very little.

Case 9. This case, followed for ten months before death, was also typical of Group 1 H. S., a 50 year old taxi driver with a body surface area = 1.66 m., had been in good health except for well controlled diabetes and a slight chronic productive cough of three years' duration until ten months before admission, when he developed an atypical pneumonia, involving the lower half of the right lung. Following six weeks of hospitalization he was unable to work because of weakness and rapidly progressive and disabling dyspnea. Seven

and eight months after his pneumonia he was treated for congestive failure at two other institutions. At the time of admission to the hospital a few weeks later he was extremely cyanotic and dyspneic at rest. The chest was greatly increased in the anterior-posterior diameter and its expansion markedly limited. The breath sounds were distant and there were coarse persistent rales at both bases. The liver, at first not large, later became palpable four finger breadths below the costal margin. Hemoglobin 20.3 grams, red blood cells 7,800,000, plasma volume 2,000 cc per square meter body surface. Some relief was obtained from phlebotomy and digitals. He was readmitted to the hospital three times during the following ten months. His congestive symptoms progressed rapidly and he died ten months after his first admission, eighteen months after his original attack of pneumonia. X-ray of the chest (fig 5) revealed considerable hyperaeration of the lung fields. The heart was not enlarged, although dilatation of the pulmonary conus and ar-

TABLE 10

Physiological Measurements in a Case of Chronic Pulmonary Emphysema with Cardio-pulmonary Insufficiency

	CASE 9	
	Observed	Predicted
1 Lung volumes in cc		
Vital capacity	2090	3720
Residual air	2724	1650
Total capacity	4814	5370
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	57	30
2 A Maximum breathing capacity in L/min		
Before bronchodilator	24	97
After bronchodilator	29	
3 A Index of intra-pulmonary mixing alveolar N ₂ %	3.5	<2.5
B Arterial blood		
Oxyhemoglobin saturation %		
Basal	78	96
Carbon dioxide tension in mm Hg		
1st min recovery	62.3	43.7

teries was conspicuous. Both diaphragmatic leaves were flattened and depressed with marked blunting of the costo-phrenic sulci. The electrocardiogram showed right axis deviation and evidence of myocardial damage.

The physiological studies are summarized in table 10. As can be seen, there was an extreme limitation of the maximum breathing capacity with no improvement following bronchodilator spray and a marked arterial anoxia and carbon dioxide retention at rest. Because of the very poor state of the patient when these studies were made, they were limited to the resting state.

Autopsy Both lungs showed numerous small bullae ballooning under the visceral pleura. There was marked honeycombing of the cut surface of the lung, which showed many irregular cavities with unusually prominent blood vessels as the lung collapsed about them. Considerable broncho-pneumonia was present in both lower lobes. As seen in the microscopic section (fig 6) the alveoli are greatly enlarged with loss of alveolar septal

walls and coalescence of the alveoli to form large saccular spaces. The alveolar walls, elsewhere, are greatly thinned and appear bloodless. The blood vessels show intimal proliferation with narrowing of the lumina, medial degeneration and calcification. Elastic tissue stains reveal almost complete loss of elastic tissue. The heart weighed 440 grams. There was marked dilatation and hypertrophy of the right auricle and ventricle, and only

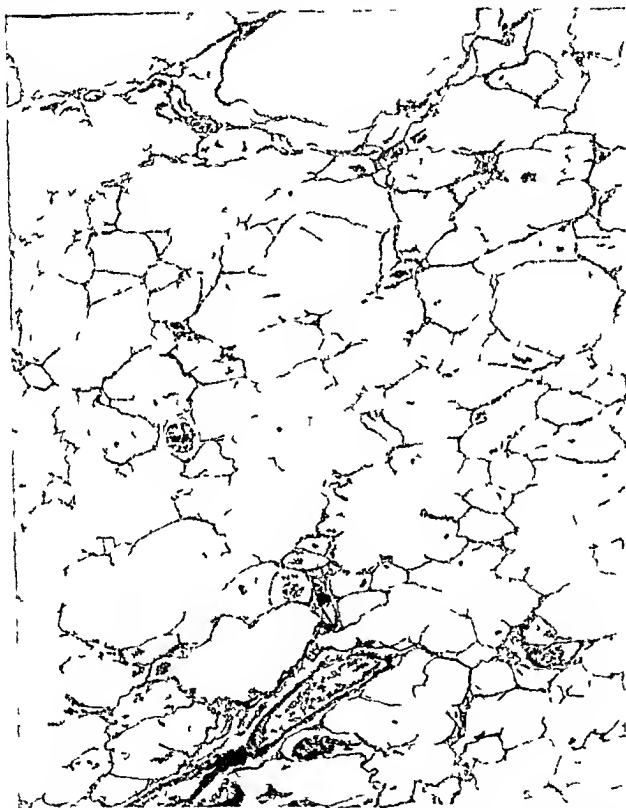


FIG. 6. MICROSCOPIC SECTION OF THE LUNG SHOWING THE CHARACTERISTIC HISTOLOGICAL FINDINGS IN PATIENT H. S. (CASE 9).
For description see text.

slight dilatation of the pulmonary artery. Chronic passive congestion of the liver and spleen was present.

Relationship between the sparse physiological observations and some of the autopsy findings is worth discussing. The marked loss of pulmonary elasticity rather than reversible bronchiolar obstruction, well explains the poor response to bronchodilators. The extensive shrinking of the pulmonary vascular bed due to atrophic changes, with the additional fac-

tors of anoxia and polycythemia, contributed probably to the development of cor pulmonale. The extent of the disintegration of the lung parenchyma may well explain this patient's rapid and progressive downhill course in contrast to the prolonged and chronic course of the preceding case. The reasons why pulmonary arteriolar sclerosis was present in this case and not in the preceding one are not clear.

These studies illustrate clearly that varying anatomic changes may produce similar functional disturbances. From the clinical and physiological point of view both cases presented the classical picture of obstructive emphysema, cor pulmonale and right heart failure. Anatomically the first case was predominantly one of cor pulmonale in chronic congestive failure with only moderate pulmonary emphysema, whereas the second was predominantly atrophic pulmonary emphysema with a definite but less striking cor pulmonale. Severe disturbances of the ventilatory and distributive functions of the lungs may apparently result as readily from marked engorgement of the pulmonary vascular bed as from loss of pulmonary elasticity or atrophic changes. Besides structural changes in the lung leading to a considerable reduction in the size of the vascular bed, other physiological factors, such as polycythemia, would seem to contribute to the development of right ventricular hypertrophy and failure.

DISCUSSION

The data presented in this paper raise a number of questions concerning the relationships existing among the various measurements, the correlation between the extent of the pathological process and the disturbance in the physiological adjustments, and the importance of the physiological observations in helping direct the treatment.

a) Relationship between vital capacity and maximum breathing capacity

In contrast to the findings of Knipping et al (3, 4) our data as shown in figure 11, fail to indicate any close correlation between the variation of the vital capacity and of the maximum breathing capacity. As a rule, the reduction in maximum breathing capacity in these cases of emphysema is greater than the reduction in vital capacity, in contradistinction to the findings noted in the group of pulmonary fibroses with alveolo-respiratory insufficiency previously reported (14). Therefore, factors reducing air flow velocity, such as bronchiolar obstruction, destruction of elastic fibers, mechanical disadvantage and poor coordination in the functioning respiratory muscles appear to be of greater significance in restricting maximum breathing capacity in the course of emphysema, than do the reduced spatial limits within which maximum ventilation is performed.

From the practical point of view the observations made in these two important groups of chronic pulmonary disease thus limit the usefulness of vital capacity as a measure of ventilatory function.

b) Relationship between $\frac{\text{breathing reserve}}{\text{maximum breathing capacity}}$ ratio and dyspnea

A number of observers have previously noted a correlation between the available breathing reserve and the development of dyspnea. Two of the

present authors have shown that the threshold of dyspnea is reached usually when the breathing reserve falls to values between 60% and 70% of the maximum breathing capacity (15). This relationship has been tested in normal subjects and in patients with a variety of chest lesions, after thoracoplasty and resection of the lung and in chronic pulmonary fibrosis. In most patients reported here, however, the threshold of dyspnea has been found to be much lower than hitherto observed. In the 4 different groups the average breathing reserve reached during

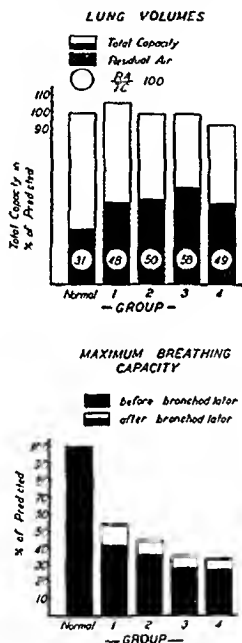


FIG. 7. AVERAGE MEASUREMENTS OF TOTAL LUNG VOLUME AND OF MAXIMUM BREATHING CAPACITY IN 4 GROUPS OF PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA.

the first minute following the cessation of dyspnea, respectively 56, 41, 34 and 39 per cent of the maximum breathing capacity.

The cause of this unique discrepancy in our experience is probably of a psychological nature. Oftentimes in patients belonging to the anoxic groups, dyspnea is already present at rest. During exercise and early recovery they first complain of intense discomfort bordering on the feeling of suffocation, after a more or less prolonged period they often signal that dyspnea is over, although the ventilation may still be significantly larger than during quiet breathing. Whether this paradox is related to the contrast between the unbearable feeling of suffocation and a relatively more easy state of breathing, or to the blunting

of sensations as a result of the effects of acute anoxia and high carbon dioxide tension upon the cerebral cortex can only be surmised

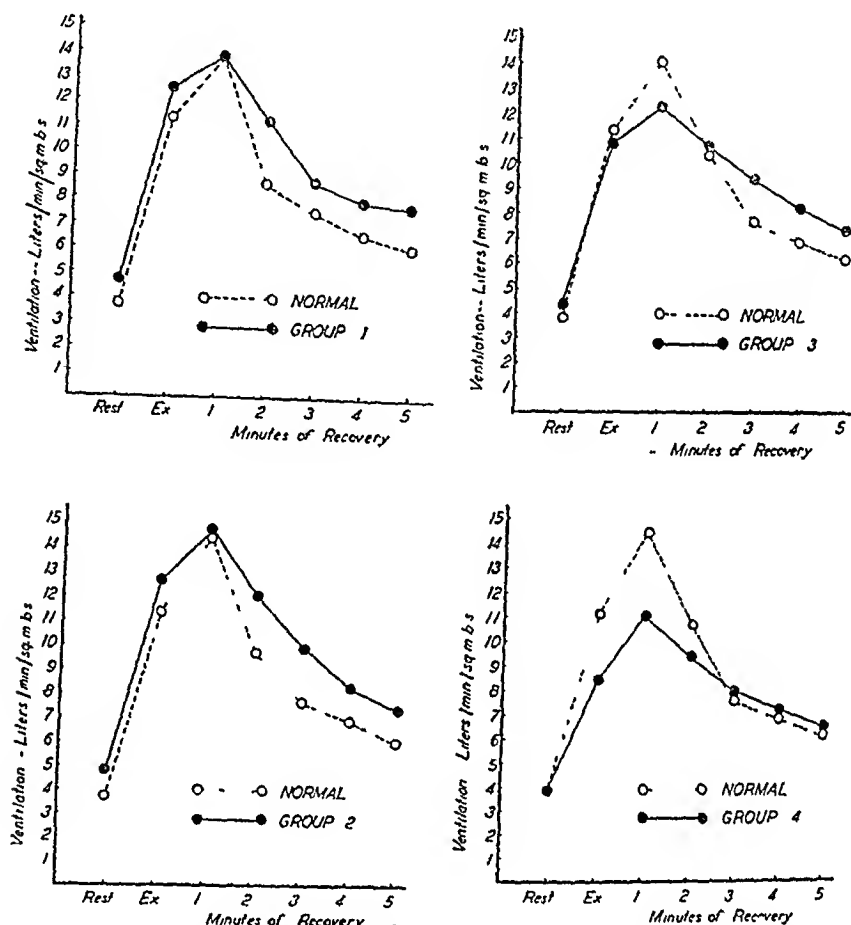


FIG 8 AVERAGE MEASUREMENTS OF VENTILATION AT REST DURING THE STANDARD EXERCISE TEST AND DURING THE FIRST 5 MINUTES OF RECOVERY FOLLOWING EXERCISE IN 4 GROUPS OF PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA

c) Relationship between the residual air/total capacity ratio $\left(\frac{R A}{T.C} \times 100\right)$ and the arterial blood oxygen saturation

In their group of 27 patients with chronic pulmonary emphysema, Huitado, Kaltreider and McCann (11) observed a close correlation between the extent of the pathological process as judged from the residual air/total capacity ratio $\left(\frac{R A}{T.C} \times 100\right)$ and the degree of reduction of the arterial blood oxygen saturation. This view is apparently confirmed by comparing the mean values for both these measurements in Groups 1, 2 and 3 where the arterial oxygen saturation decreases as the residual air/total capacity ratio $\left(\frac{R A}{T.C} \times 100\right)$ increases. In Group 4, however, where this ratio is equal to that in Group 1, the arterial oxygen saturation is the lowest in all groups. Furthermore, examination of

figure 12, where both measurements have been plotted against each other in 91 cases of chronic pulmonary emphysema, reveals no close correlation. This lack of correlation is not altogether surprising. Our classification indicates that, aside from the effect of pathological changes on the alveolar ventilation-perfusion relationship prevailing throughout the lungs, physiological adjustments involved in the regulation of total ventilation must play an important

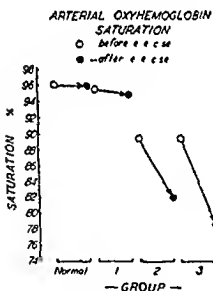
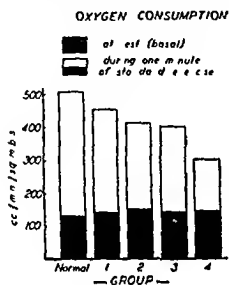


FIG 9

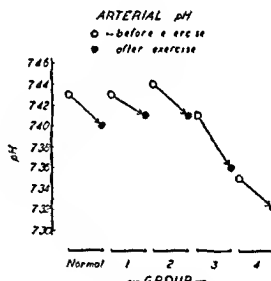
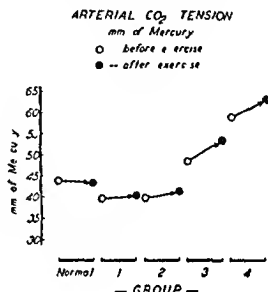


FIG 10

FIG 9 AVERAGE MEASUREMENTS IN OXYGEN CONSUMPTION AND ARTERIAL OXYHEMOGLOBIN SATURATION AT REST AND IN RELATION TO EXERCISE IN 4 GROUPS OF PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA

FIG 10 AVERAGE MEASUREMENTS OF ARTERIAL CO₂ TENSION AND ARTERIAL pH AT REST AND AFTER EXERCISE IN 4 GROUPS OF PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA

part in the variation of arterial blood oxygen saturation. For an adequate analysis of the factors involved in the regulation of the arterial blood oxygen saturation, it appears essential to determine also the magnitude of alveolar ventilation. Total ventilation, intrapulmonary mixing, and carbon dioxide tensions must therefore be taken into account, and also the various physiological adjustments involved in the regulation of ventilation. It is on the basis of

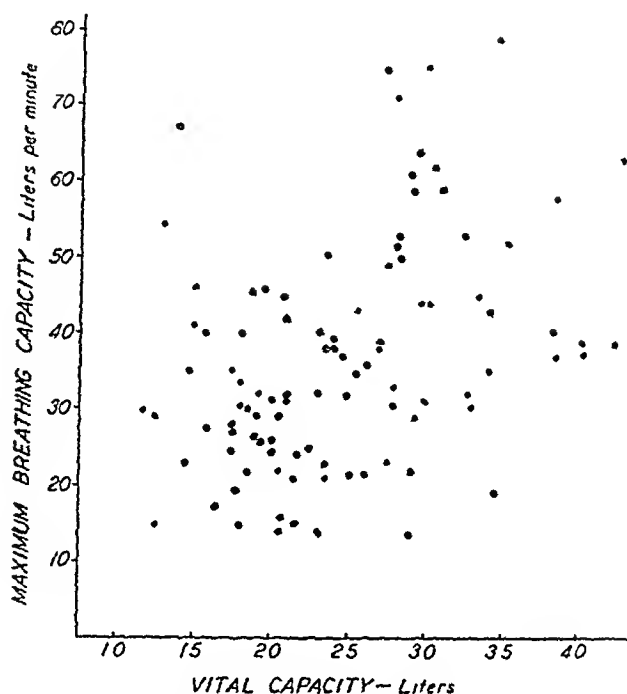


FIG 11 CORRELATION BETWEEN MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY IN 100 CASES OF CHRONIC PULMONARY EMPHYSEMA
For discussion see text

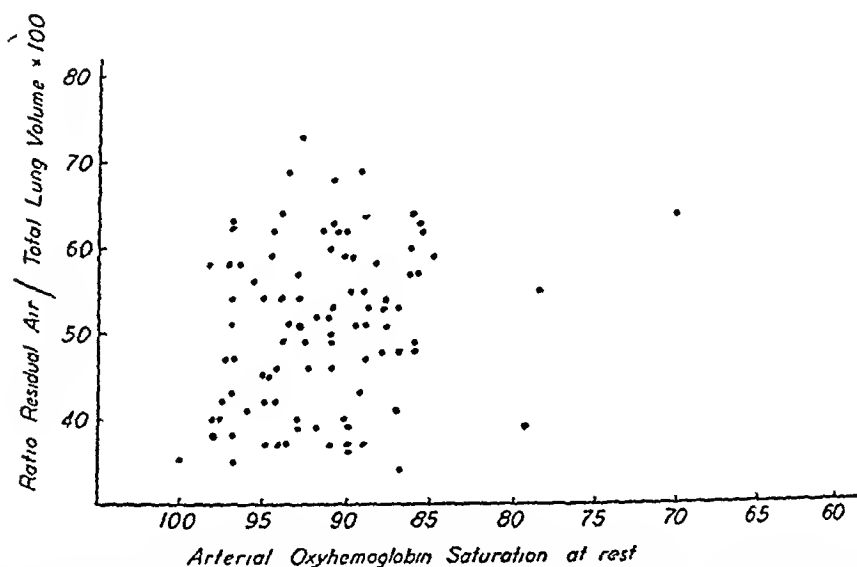


FIG 12 CORRELATION BETWEEN RATIO RESIDUAL AIR/TOTAL LUNG VOLUME $\times 100$ AND ARTERIAL OXYHEMOGLOBIN SATURATION AT REST IN 92 CASES OF CHRONIC PULMONARY EMPHYSEMA
For discussion see text

such considerations that the present physiological classification has been attempted and that comments have been repeatedly made in the course of this paper concerning the physiological responses prevalent in each group

d) Relationship between 1) the measurements of the oxygen debt and of the oxygen consumption during exercise and 2) cardiac insufficiency

Nylin (16) has shown previously that an increase in the oxygen debt following a standard exercise test of short duration, is a reliable index of cardiac insufficiency. Comparison of the data obtained in two of our groups with approximately the same degree of anoxia following exercise (Groups 3 and 4) fails to show any difference in their oxygen debt, although Group 4 presented clinical manifestations of cardiac failure. To account for the difference between Nylin's and our observations it should be pointed out that the methods of calculating the oxygen debt and the degree of severity of the exercises used differ significantly from one another. The standard exercise step test used in these studies is of shorter duration and involves less strain, and the oxygen consumption is measured during the entire first 5 minutes of recovery, whereas in Nylin's test, the oxygen consumption is measured from the second minute of recovery on up to and including the sixth minute. If, therefore, patients with isolated pulmonary insufficiency repay during the first minute of recovery some of their oxygen debt at a larger rate than patients with cardio-pulmonary insufficiency, the difference in response of the two groups of patients would be more apparent in Nylin's than in our figures.

From the figures obtained in these same groups, 3 and 4, it would appear that the measurement of the oxygen consumption during the standard step exercise test provides an excellent means of detecting the presence of cardiac insufficiency in emphysematous patients.

e) Relationship between arterial anoxia and polycythemia

One of the striking findings in these studies is the observation that polycythemia is usually not present in patients with pulmonary insufficiency regardless of the severity of the anoxia, unless there is evidence of chronic cardiac failure. Beyond this, our data do not provide any further information concerning the influence of chronic pulmonary insufficiency upon the development of polycythemia. It is even difficult at times to deduce which is the primary and which the secondary effect. Further studies are needed on this interesting problem.

f) Relationship between silicosis and chronic pulmonary emphysema

Nine cases of silicosis complicated by chronic pulmonary emphysema were included in these studies. Their pulmonary function pattern did in no respect differ from that observed in the other cases. All presented a severe restriction of the maximum breathing capacity to 22 to 45 per cent of the predicted value. Five of the cases with a normal arterial oxygen saturation at rest and following exercise had a total lung capacity greater than the predicted value, whereas the four remaining cases, presenting severe arterial anoxia, showed a considerable restriction in their total lung capacity. The physiological disturbances were not correlated with the roentgenological findings. Diffuse nodular infiltration as well as conglomeration of silicotic nodules were present in both groups irrespec-

tive of the extent of the pulmonary insufficiency As has been noted by many observers, the severity of pulmonary insufficiency in silicosis is greatly increased by the presence of a coexisting emphysema This is true only because obstructive emphysema, whatever its etiology or its extent, profoundly disturbs both the ventilatory and alveolar respiratory function of the lungs The eight cases of silicosis included in the group of uncomplicated pulmonary fibrosis described in the second paper of this series, presented in contrast moderate ventilatory insufficiency without obvious disturbance to the intrapulmonary distribution or diffusion of the respiratory gases

g) Remarks concerning the treatment of emphysema

The treatment of pulmonary emphysema is notably unsatisfactory and discouraging. The elimination of infection in the upper respiratory tract, prophylaxis against respiratory infections and the limitation of the patient's physical activities are measures that require no comment On the other hand, the bronchodilator drugs are usually reserved for acute asthmatic episodes or the severely disabled patient Yet spirographic tracings show that the mildly emphysematous patient, as well as the asthmatic patient, usually performs the maximum breathing capacity in a state of hyperinflation After use of a bronchodilator spray more rapid ventilation can be performed in a state of lesser pulmonary inflation. The continued daily use of bronchodilators, therefore, is of value in relieving bronchiolar obstruction, and diminishes the tendency to hyperinflation Several of our patients have used "vaponefrin"² spray for years without harm and with considerable benefit Autopsies on two such patients, who used "vaponefrin" continuously for nine and four years respectively, revealed no pathology of the bronchial mucosa that could be ascribed to the prolonged action of this drug The daily inhalation of a bronchodilator must be considered harmless and probably beneficial and should be encouraged in patients that show objective spirographic improvement with such therapy It should be noted, however, that a few patients cannot tolerate this drug because of bronchial irritation or mild systemic effects, others can use it only sparingly

Oxygen therapy, likewise, can be extremely beneficial to patients with emphysema, when properly administered As a relief to acute anoxia following a relatively mild respiratory infection it is mandatory and may avert the development of acute congestive failure or asphyxia It is well known, however, that patients with chronic anoxia become well acclimated to a low blood oxygen tension and may exhibit neither mental nor physical signs referable to it Such patients given oxygen over a prolonged period frequently lost this compensation, so that it became impossible to wean them from the oxygen tent or mask These findings have properly discouraged the use of continuous prolonged oxygen therapy in emphysema On the other hand, intermittent inhalation of high oxygen for 15 to 30 minutes three or four times a day often results in subjective improvement, diminution of weakness and fatigability, improvement of appe-

² Supplied by Vaponefrin Company, 6816 Market Street, Upper Darby, Pa This is a solution containing epinephrin-like substances

tite and increased sense of well being. Even such treatment should be approached with caution in patients belonging to Group 4. In some of these patients (see table 11) the inhalation of 100% of oxygen for even a short time will result in further depression of the ventilation, excessive retention of carbon dioxide (blood CO_2 up to 90 or 100 volumes per cent), and increasing acidosis. Bereonsky (9) had previously observed these effects of oxygen therapy in two similar groups of patients. The following mechanism is probably responsible for these changes. As the oxygen tension in the arterial blood increases, the stimulation of the carotid body is reduced, causing hypoventilation. Hypoventilation in turn is responsible for carbon dioxide retention, with its accompanying signs of mental confusion and even coma. These manifestations usually are ascribed to oxygen poisoning, although they are related to carbon dioxide narcosis. It would seem that the combined use of an intermittent pressure breathing device in order to maintain ventilation, with oxygen therapy, might avert the latter complication in this group of cases.

TABLE 11

Influence of Oxygen Therapy Upon the Ventilation and the Carbon Dioxide Tension and pHs in 3 Cases of Chronic Pulmonary Emphysema with Cardio pulmonary Insufficiency

VENTILATION L/MIN/M ² B.S.		CARBON DIOXIDE OUTPUT CC/MIN/M ² B.S.		ARTERIAL OXYGEN SAT- URATION % PER CENT		ARTERIAL CO_2 TENSION, MM Hg		ARTERIAL pHs	
Before	After	Before	After	Before	After	Before	After	Before	After
4 26	3 41	171	165	57	100	54 0	73 5	7 34	7 23
4 35	3 50			75	102	54 0	72 0	7 41	7 28
4 02	3 56	168	144	71	102	53 0	61 0	7 40	7 35

In the same group of patients with polycythemia and cardiac failure the use of phlebotomy repeated at frequent intervals has been rewarding. In one patient of this series (M. K.) a total of 16 phlebotomies amounting each to from 750 cc to one liter were performed over a period of 5 years.

SUMMARY

1 A physiological classification of chronic pulmonary emphysema is proposed, in which cases with pulmonary insufficiency and those with cardio-pulmonary insufficiency are considered separately. The severity of pulmonary insufficiency was judged from the reduction of the arterial oxygen saturation and from the increase in carbon dioxide tension following a standard exercise test.

2 Four groups were thus defined.

a In Group 1 severe impairment of the ventilatory function and moderate disturbance of intra-pulmonary air distribution are present. Hyperventilation, however, adequately compensates for the disturbance of distribution, thus maintaining an adequate alveolar ventilation with normal respiratory gas exchange and preventing the development of arterial anoxia. The major disa-

bility of this group, therefore, is the reduction in breathing reserve, which limits physical activity and causes dyspnea

b In Group 2 impairment of the ventilatory function and greater disturbance of air distribution appear. Although hyperventilation still maintains a relatively normal arterial carbon dioxide tension, the compensation is not sufficient to prevent arterial anoxia at rest and following exercise. To the reduction in breathing reserve another major disability is thus added in this group, namely, alveolo-respiratory insufficiency.

c In Group 3 the reduction of ventilatory function and the disturbance in air distribution are both marked. Compensatory hyperventilation during exercise and early recovery is not possible because of the limitation of the ventilatory capacity. This adds to the inadequacy of the alveolar ventilation as a cause of the arterial carbon dioxide retention and arterial anoxia. This group suffers from profound ventilatory and alveolo-respiratory insufficiency.

d In Group 4 a ventilatory and an alveolo-respiratory insufficiency nearly as severe as in Group 3 is associated with evidence of polycythemia and chronic congestive heart failure. Hypoventilation during all the periods of observation in the presence of a high arterial carbon dioxide tension and acidosis, and a low oxygen saturation are striking features of this group. They reveal a profound disturbance in the response of the respiratory centers to normal stimuli.

3 Individual cases, some of them with autopsy findings, have been described in order to illustrate further the characteristic patterns of pulmonary dysfunction observed during the course of the disease.

Grateful acknowledgment is made to Dr David Spain and other members of the Department of Pathology (Columbia University), to the various physicians and technicians who contributed over many years to the collection of the data and to Dr John West, who prepared four charts.

The authors wish to direct attention to the following typographical errors in the first paper of this series:

(a) page 253, bottom, should read

V = volume of expired air under spirometer, etc

(b) page 267, bottom, should read

$86.5 - [0.522 \times \text{age in years}]$

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PHAGOCYTOSIS

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TABLE OF CONTENTS

1 Mechanisms of Phagocytosis	240
2 Methods of Studying Phagocytosis	242
3 Physical Factors Modifying Phagocytosis	245
a The effect of temperature	245
b The effect of x rays	246
c The effect of electric charge	247
4 Chemical Factors Modifying Phagocytosis	248
a Sulfanamides	248
b Gastric mucin	252
c Natural and artificial opsonization	253
(1) In vitro experiments	253
(2) In vivo experiments	255
5 Phagocytosis Changes in Starved Blood	257
6 The Role of Nutrition in Phagocytosis Activity of Tissues	259
7 Other Factors Modifying Phagocytosis	262
a Nervous stimulation	262
b Endocrines	262
c Leukemia	264
d Anemia	265
e Miscellaneous factors	268
8 The Phagocytic System as a Tool	270
a In testing antiseptics	270
b In diagnosis of brucellosis	271
c In testing the immune reaction in pertussis	272
9 The Role of Phagocytosis in Disease	272
a Pneumonia	272
b Tuberculosis	274
c Streptococcus infections	276
d Protozoan infections	278
(1) Malaria	278
(2) Trypanosome infections	279
(3) Spirochaete infections	280
e Helminthic infection	280
f Virus infections	280
10 Phagocytosis and Immunity	281
a The importance of strains in determining bacterial susceptibility to phagocytosis	281
b Anti phagocytic substances	283
c The fate of ingested particles	284

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11	Studies on the Phagocytic Behavior of the Cells of the Reticulo-endothelial System	
	a Macrophages	285
	b Microglia	285
12	Phagocytic Functions in Lower Animals	286
	a Lower vertebrates	287
	(1) Chick embryos	287
	(2) Amphibians	288
	(3) Fish	289
	(4) Cyclostome	289
	b Invertebrates	289
13	Discussion	290
14	Summary	292
15	Bibliography	294

Since the classical work of Metchnikoff the importance of the cellular defense mechanism has been recognized. The numerous investigations on various aspects of the subject that appear each year in the world's literature serve as convincing evidence for a general recognition of the necessity for thoroughly understanding this phenomenon. Both because of this interest in phagocytosis as well as the great diversity of approach in experimentation, it was deemed worthwhile to attempt this review. Mudd, McCutcheon and Lucké (210) and previously Mudd (209) presented excellent summaries of the work up to 1934, especially in regard to the mechanism of phagocytosis. Earlier reviews are cited by these authors. More recently Cannon (39) has analyzed the functional significance of the humoral defense mechanism which, as he points out, may aid the cellular defense forces, and Robertson (248) has reviewed the process of phagocytosis of foreign material in the lung. The present report will be limited to those aspects of the subject not treated by the above authors.

1 Mechanisms of Phagocytosis

The ingestion of particles by phagocytes, according to the formulation of Fenn (discussed at some length by Mudd et al, 210), is the result of interplay of surface forces which may be considered as surface tension or surface energy. In either case the end result on ingestion of a particle is a lowering of the free energy of surfaces. The surface tensions (or energies) of importance in this process are those between phagocyte and suspending fluid, S_1 , particle and suspending fluid, S_2 , and the phagocyte-particle interface, S_{1-2} . Thus, when a phagocyte and particle are in contact, Ponder (210) showed that ingestion occurs when

$$\frac{S_1 - S_{1-2}}{S_2} \approx \text{or} > (+1),$$

it fails to occur when the same relationship is less than or is equal to (-1) , and partial ingestion takes place when the ratio is greater than (-1) but is less than $(+1)$. It follows from these considerations that phagocytosis is favored by (1) an increase in the value of the particle-suspending fluid surface energy (a change that Mudd and co-workers (210) has shown to follow contact with specific immune serum) (2) a decrease in the value of particle-phagocyte

interfacial energy, (3) a decrease in phagocyte-suspending fluid surface energy, or (4) a combination of any of these. Therefore, from the thermodynamic point of view phagocytosis should be a spontaneous process not requiring a net expenditure of energy on the part of the cell accomplishing the engulfment. If this concept is correct, and most of the experimental evidence suggests that it is, one should not necessarily expect a metabolic change to occur during active phagocytosis unless some change results after the particles are inside the phagocytes. Only two publications dealing with this subject are available. Baldrige and Gerard (14) working with dog leucocytes suspended in dog serum found an increase in oxygen consumption after the addition of a suspension of *Sarcina lutea*. This was measured manometrically and a burst lasting 10-15 minutes to values twice the resting rate of oxygen uptake was followed by a gradual return to normal values over a period of $1\frac{1}{2}$ to $2\frac{1}{2}$ hours. Active phagocytosis was demonstrated. There was no respiratory change accompanying the ingestion of India ink. In the same year, Ado (2) also using the Warburg respirometers, observed no change in aerobic respiration when starch, India ink or a suspension of dead *B. coli* were added to leucocytes from guinea pigs, rabbits or dogs. Glycolytic activity of the white cells was reduced by 50%, however, beginning about 20 minutes after the addition of the particles. Additional work along these lines is needed.

Since phagocytosis is best explained as a surface energy phenomenon, it is reasonable to suspect that surface active compounds should exert a profound effect on the process. With this in mind, Leyendecker and Berry (174) tested the effect of several detergents on phagocytosis in vitro. Sodium glycocholate and zephiran chloride in concentrations of 0.0001% by weight increased the mean number of bacteria ingested by 100 human leucocytes by 40% over the value for controls. On the strength of these results Berry, Starr and Haller (23) selected the most potent phagocytosis-promoting detergents from a group of sixty that were tested. Five, decyl benzene sodium monosulfate, carboxymethylcellulose, hydroabietyl sodium sulfate, Triton N-100 and Tween 20, were capable of approximately doubling the mean number of bacteria ingested by neutrophils as compared with normal controls. This is shown in Table I. The first three are anionic and the last two are non-ionic detergents. Some cationic surface active agents enhanced phagocytosis but none was as effective as those listed. Subsequent tests proved that these compounds were equally effective when phagocytosis was evaluated as per cent of leucocytes active. Comparable results were obtained with both human and mouse blood. It was also observed that the detergent (Triton N-100 in this case) injected intraperitoneally in mice was capable of enhancing the phagocytic power of the blood leucocytes tested in vitro. Injections repeated at 4 hour intervals for 3 days maintained the leucocytes in the hyperactive state as determined by the periodic in vitro tests on shed whole blood. This increased phagocytic activity was unable to confer any protection to the animals against experimentally induced mouse typhoid, comparable to that observed in earlier work by Berry and Haller (22) in the case of anemic mice (see section 7d). An explanation for the

therapeutic failure of Triton N-100 was readily obtained when the *in vitro* experiments were extended to include preliminary incubation of the bacterial cells (either *Staph. aureus* or *Sal typhimurium*) with the detergent before adding them to the blood rather than the reverse procedure previously followed. When this was done phagocytosis was depressed, but when bacteria and blood were each incubated with the detergent prior to mixing, phagocytic values were almost identical to those found for controls. These results are not only explained by Fenn's formulation as interpreted by Ponder (210) but offer the strongest kind of evidence for its validity. For example, when the surface "tension" (surface energy) of the leucocyte is lowered, phagocytosis is increased but when the surface "tension" of the bacteria is lowered, phagocytosis is decreased. When both are lowered proportionately, no change in phagocytosis results.

TABLE I
Detergents Tested in Vivo
from Berry, Starr and Haller (23)

DETERGENT	PH	PHAGOCYTIC COUNTS					% PHAGOCYTOSIS				
	1	2	3	4	5	6	7	8	9	10	11
	01%	0005%	00005%	000005%	Control		Prob		Prob		Prob.
Anionic											
1 Decyl benzene Na monosulfate	5 04	8 18 ± .23	3 94 ±	2 6 14 ±	2 3 82 ±	2 214	< 01%	103	36 34%	160	< 01%
2 Carboxymethyl cellulose	5 47	8 13 ±	2 6 09 ±	3 5 06 ±	2 4 06 ±	2 200	< 01%	150	< 01%	124	29%
3 Hydroabietyl Na sulfate		4 59 ±	2 2 90 ±	1 3 24 ±	1 2 34 ±	1 177	< 01%	131	6 68%	158	< 07%
Non-ionic											
4 Triton N-100	5 14	6 19 ±	2 4 75 ±	2 4 98 ±	2 2 47 ±	1 250	< 01%	192	< 01%	201	< 01%
5 Tween 20		4 64 ±	2 3 82 ±	2 4 61 ±	2 2 54 ±	2 227	< 01%	195	< 01%	183	< 01%

More recently a new type of phagocytosis has been described in some detail by Wood and his collaborators (316, 317) in connection with their work on recovery in pneumonia. Ingestion of pneumococci by lung phagocytes in the absence of circulating antibodies has been attributed to the surface contact between the cells and bacteria and has been termed "surface phagocytosis." This will be considered in the light of the Fenn formulation after the experimental details have been presented in section 9a.

2 Methods of Studying Phagocytosis

There are two basic procedures in general use for the quantitative evaluation of phagocytosis *in vitro*. In one, the average number of particles engulfed per leucocyte in a given time period is determined and in the second the percentage of leucocytes showing engulfment of particles in a given time is found. The former method is attributed to Wright and the latter to Hamburger (210). Since contact between phagocyte and test particle is the first event that must occur in order for the particle to be ingested any method must, by agitating the mixture, insure contact, assuming the absence of, or a variable, chemotaxis.

Moreover, it is apparent that under theoretically ideal conditions in which all test particles and leucocytes are single and uniformly distributed throughout the experimental fluid the two methods should be numerically proportional. Because such an ideal distribution of particles, especially bacteria and probably phagocytes, is impossible to realize it can be shown statistically (281) that the Hamburger procedure is the better since the size of the clumps loses its importance. It is frequently true, however, that the two methods yield results that are in good agreement (cf 23).

Boerner and Mudd (28) described the method of evaluating the phagocytic power of whole blood or of plasma-leucocyte mixtures which, with some minor modifications, is generally employed today. Heparin, as an anticoagulant, replaced those which had previously been used and which precipitate the calcium ion, now known to be important in phagocytosis. An agitator provided a continuous mixing of the cells and test objects at constant temperature. Phagocytic activity was determined by microscopic examination of stained smears and the overall reliability of the method was shown statistically. In cases where only small volumes of blood are available Kossovitch and Canat (167) used a technique in which the blood was collected in an ordinary white cell pipette (about 20 cubic millimeters). The white cells were separated by centrifugation in a special bulb tube without the use of an anticoagulant. The cells and culture to be tested were mixed and incubated, after which the few remaining erythrocytes were lysed with dilute acetic acid. Smears were then made and stained with Bismarck brown. It is doubtful if this procedure is as quantitative or as reproducible as one in which larger volumes are employed. The mixing is probably less thorough with such small volumes and the proportion of leucocytes to test particles is probably subject to larger variations.

The importance of leucocyte counts in carrying out phagocytic tests was emphasized by Jung (155), especially when comparison between samples of blood from different sources or from the same individual at different times is desired. A more thorough treatment of the same problem is found in the work of Hanks (130). He showed that unless the relative number of bacteria and leucocytes as well as the number of each per unit of volume was controlled, test values for either percent of leucocytes showing ingestion or the average number of bacteria per phagocyte were subject to misinterpretation. It is only when two or more sera were compared simultaneously against the same suspension of bacteria and leucocytes that such considerations may be neglected. As bacterial numbers increased, while holding the number of phagocytes constant, the values for bacilli-per-leucocyte changed as a linear function of the number of bacteria while the percentage phagocytosis values changed with the logarithm of bacterial numbers. These relationships held over the range investigated. The effectiveness of the phagocytic system, which measures the percentage of available bacteria engulfed, decreased as the number of bacteria and the phagocytic values rose. With constant numbers of bacteria, an elevation in the number of leucocytes increased the effectiveness but lowered the percentage phagocytosis and bacteria per leucocyte values. As the numerical density of the system in-

creased, but with a constant ratio between the number of bacteria and white blood cells, higher phagocytic values and increasing action of the leucocytes on the bacteria during unit time resulted. Since ingestion did not keep pace with increasing probability for collision between bacteria and leucocytes when bacterial numbers increased in the presence of a constant number of leucocytes, Hanks suggested that there was less adequate sensitization of the bacteria and that undetermined physical factors were possibly responsible.

All quantitative methods of evaluating phagocytosis make use of leucocytes whose activity is measured *in vitro*. This is done despite the fact that the fixed phagocytes of the reticulo-endothelial system are known from numerous qualitative experiments to be of primary importance in the removal of some foreign particles from the blood stream (see sec. 11 of this paper). Thus the demonstration by Maxfield and Mortensen (196) that radioactive thorium may be used in quantitatively evaluating the phagocytic action of these cells opens up a new avenue of approach to their study. Colloidal thorium dioxide was injected intravenously into rabbits, 1 cc per kilo body weight. The number of particles, n , decreased with time according to three distinct exponential laws. The system was apparently overloaded at first but when n reached about one-sixth its initial value, the fraction removed in unit time increased. More than 99% of the thorium was removed from the blood stream in 6-8 hours. Mathematical analysis indicated that when the system was not overloaded (corresponding to the last two exponential laws) the foreign matter was removed according to the equation

$$n = n_0 e^{-at} + (b/2a) n_0 e^{-bt}$$

where n_0 is the number of particles initially present, n is the number of particles remaining in the blood after time t , and where $a \gg b$

$$a = \alpha + \beta \text{ and } b = \alpha \gamma / \alpha + \beta$$

and α is the fraction of the amount present which is permanently disappearing in unit time, β is the fraction of the amount present which is disappearing temporarily in unit time and γ is the fraction of the amount temporarily removed that is reappearing in unit of time. It is believed that this technique will find wide use in following the changes in rate of phagocytosis of particles by cells of the reticulo-endothelial system under numerous experimental conditions. However, the effect of thorium itself must first be thoroughly investigated and proven to be a suitable material for testing the ingestion of particulate matter. There is already available the work of Wen and Jung (305) in which the reaction of blood and tissue cells toward colloidal thorium dioxide (thorotrast) has been studied. These authors found that intravenous injection of thorotrast was followed during the early phase of the reaction by an increase in number of monocytes and neutrophils, both active in phagocytosing the particles. Liver cells and suprarenal cortical cells also took up some of the fine granules while the cells of the reticulo-endothelial system engulfed them as large masses. The latter cells, together with the monocytes, frequently fused with each other to

form foreign body giant cells Barbieri (15) also observed the formation of what he termed large granular syncytial islands in the liver, spleen and bone marrow when certain cells in these organs became stuffed with thorium granules. Some of these, according to Wen and Jung, became separated and were carried away with the blood to be eliminated through the lungs but most of them persisted in the spleen, liver, bone marrow, etc for a considerable time. When either trypan blue or lithium carmine were injected intravenously after the thorotrast had been given, the cells were still capable of taking up the dye particles. This proves that the reticulo-endothelial system was not "blocked" by the thorium dioxide. Subcutaneous injections of thorotrast were always followed by a migration of a large number of neutrophilic leucocytes from the blood vessels to the connective tissue. These, together with the clasmatoocytes and fibroblasts, were phagocytically active. There was a great variability in the ingestive capacity of the neutrophiles which was believed to be due to the availability of the thorium in the injected region. The clasmatoocytes and fibroblasts reacted in much the same way toward this material as they did to intra-vital acid dyes. Subcutaneous injections of both thorotrast and dye showed that more dye was taken up by the various phagocytic cells than thorium granules. This may have been due to the more rapid spread of the dye than of the other material. Pohle and Ritchie (236) found no impairment in the health of dogs over a period of two years following injection of thorium dioxide. Gordon and Katsh (112) have recently emphasized the value of this agent in determining the phagocytic activity of splenic macrophages in rats (see section 7a). In contrast to these findings Hanke (128) (129) and Rischke (247) claimed that the reticulo-endothelial system could be blocked by injections of thorium dioxide. However, these workers used relatively large doses and were uninterested in following the disappearance of the material after it was injected. They were attempting to overload the phagocytic cells and as Rischke pointed out, this could also be accomplished with India ink, trypan blue and other substances sometimes used to evaluate the phagocytic activity of cells. On the strength of these experiments, it therefore appears that colloidal thorium is handled in essentially a normal way by the body cells.

3 Physical Factors Modifying Phagocytosis

1. The effect of temperature. The earlier work on the effect of temperature on phagocytosis is considered by Mudd, McCutcheon and Lucké (210).

Chadani (43) studied the influence of temperature on the phagocytic function of connective tissue cells taken from living or dead animals. The tissue cells from a winter frog maintained their ability to ingest particles at higher temperatures for a shorter time than did those of a rabbit. At 30°C there was no difference and at lower temperatures the reverse held. There was a close correlation between the velocity of phagocytosis and temperature for the cells of both animals but with differences appearing for those from cold versus warm blooded animals. Tissue cells from 40 out of 55 cases of human autopsies retained their ability to phagocytose carbon particles. The longer the interval between death and autopsy, the lower the phagocytic ability of the cells.

Grunke (121) reported that artificial fever induced in human patients by the parenteral administration of a foreign protein decreased phagocytosis during the febrile reaction but that it later returned to the original activity or exceeded it. In their studies on the influence of artificial fever on the mechanisms of resistance, Ellingson and Clark (83) obtained lower specific antibody responses in rabbits when the fever was near 41.5°C but found no influence on circulating antibodies when the fever was more moderate (near 40°C). Phagocytosis of staphylococci by guinea pig leucocytes in the presence of normal serum increased with rising temperatures to a maximum of 40°C . The zone of maximal activity was from 39° – 41°C . In human blood the optimal zone for phagocytosis of staphylococci was from 38° – 40°C . On the basis of these observations Harmon, Zarafonetus, and Clark (131) undertook a more comprehensive investigation of the temperature relations of phagocytosis in vitro. Over a range of 22° – 42°C , taken in 5° increments, the phagocytic power of guinea pig exudative and rabbit polymorphonuclear leucocytes in homologous normal serum was enhanced for *Staphylococcus aureus*. The complete phagocytic system was incubated for 10 minutes in a thermostatically controlled water bath. The conclusions were based on data from 15 tests using 10 guinea pigs and 5 rabbits. In 15 experiments with mice, the results were not clear-cut because of a failure to secure an adequate leucocytic response. In a series of tests with 2° increments between 37° – 45°C , using guinea pig leucocytes and comparisons at 25° and 50°C , phagocytosis increased up to approximately 43°C and declined rapidly above this temperature. The rate of increase in phagocytosis declined as the higher temperatures were reached. In an effort to gain a clearer understanding of the mode of action of temperature on the process of phagocytosis, Zarafonetus, Harmon, and Clark (321) opsonized the bacteria (*Staph. aureus*) at one temperature and incubated the completed system at another temperature. Guinea pig exudative leucocytes and normal homologous serum were employed. Sensitization at 40°C tended to yield a slightly larger amount of ingestion at either 37°C or 40°C than did opsonization at 37°C . Phagocytosis at 40°C after preliminary opsonization of the bacteria at either 37°C or 40°C resulted in more activity than at 37°C . This is in agreement with the authors' previous results. Using 22°C and 37°C as test temperatures, opsonization was impaired by the higher temperature while phagocytosis was enhanced. These data show that phagocytosis at 37°C was decreased by any preliminary incubation of viable organisms in fresh normal serum and this inhibition was more marked at 37°C than at 22°C . There was no explanation for this observation but it was suggested that the coagulase positive strain employed might have produced an inhibitory substance comparable to that found by Hale and Smith (124).

b The effect of x-rays. Garschin, Zacharjewskaia, and Ossinskaja (96) studied the results of x-irradiating the cells of a granuloma induced in tissues by an injection of cholesterol. Three to six erythema doses were employed and the phagocytic activity of the cells was reduced. There was also a retarded infiltration of connective tissue in the foreign body deposit or probably a retarded organization, with a reduction in number, size and digestive activity of macro-

phages Jeckeln (153) found, by animal experimentation, that in the resting lymph node storage of carmin never occurred. Damage by γ ray or by injections of diphtheria toxin, however, resulted in an elevated phagocytic activity of the reticulum cells and the ingestion of dye particles. Glenn (102) measured the phagocytic indices of healthy rabbits as tested with *Staphylococcus aureus* following γ -irradiation with a 100 r dose (measured in air) delivered at 140 kv over a small area of normal skin*. There was a significant increase in phagocytosis 48 to 96 hours following the radiation. Glenn (103) continued these studies and found that the dosage originally employed produced the most marked effect and confirmed that the maximal increase comes 48 hours after treatment. A repetition of the optimal dose produced an increase in phagocytic activity which was only moderately higher than that obtained with a single dose. The index could be maintained at the higher level for only a short time. However, there was a definite tolerance of the rabbits to γ -rays for producing an increase in phagocytic function beyond which point a depression occurred. Animals previously irradiated showed a return of their phagocytic indices to normal at varying lengths of time following the treatment so that subsequent radiation following this event again produced a rise in phagocytosis which was identical with that observed in untreated animals. Glenn suggested that the therapeutic value of γ -rays in cases of infections might depend, at least in part, on this enhancement of the cellular defense mechanism. No experiments were performed to test whether the elevation in phagocytosis was due to a change induced in the leucocytes themselves or to a change in the serum's opsonizing power.

c. The effect of electric charge. This problem is more extensively treated in the earlier review (210), but several references have been found which seem worthy of discussion. Exudative leucocytes containing phagocytized chicken erythrocytes or bacteria were found by Ado (1) to have a lower electrokinetic potential than exudative leucocytes without phagocytized particles. Findlay and Brown (89) correlated the phagocytic rate with the size of the electric charge on malaria-infected erythrocytes from a canary. The lower the charge the greater was the rate of ingestion by the macrophages of the spleen. Krishnan, Chapra and Mukherjee (168) also noticed that infected erythrocytes had a lowered electric charge which they thought enhanced the ease with which the reticulo endothelial system phagocytosed the parasitized red cells. A mere reduction in charge, however, did not necessarily determine the extent of phagocytosis. The rapid changes in shape which Aleveieff (5) observed when *Entamoeba histolytica* ingested erythrocytes were attributed to changes in surface tension produced by differences in the electric charge between the cell and the amoeba. Brown and Broom (34) subsequently altered the electric charge on *Staphylococcus aureus* by means of solutions of potassium ferrocyanide and recorded a progressive decline in phagocytosis as the charge was raised. None

* Cipollaro (46) states that 300 r is equivalent to one erythema dose as measured in air with low voltage radiation. It is probable that at the voltage employed by Glenn more than 300 r would be required for one erythema dose but this would also depend upon the filter employed.

of these experiments was designed to show precisely what the authors conclude. An extremely complex inter-relationship may exist between the charge and the free surface energy of a cell or particle but the two are not necessarily proportional. If the electric charge on the surface were always directly proportional to the free energy of the surface then the relationship claimed above by Brown and Broom would always hold. However, Mudd, McCutcheon and Lucké (210) point out that in the most precise experiments dealing with this aspect of the problem, maximum charge on the particle in one case and minimum charge under a different set of conditions may give comparable phagocytic values. It may be of interest, however, to mention some unpublished results from the Biological Laboratories of Bryn Mawr College which indicated that the zeta-potential of human leucocytes suspended in physiological solution of sodium chloride was apparently inversely correlated with their phagocytic activity.

4. Chemical Factors Modifying Phagocytosis.

a. Sulfonamides. Now that the sulfonamides are known to be competitive inhibitors of the metabolism of certain bacteria, the controversy that centered around the mode of action of these drugs a decade ago assumes less significance today. It was suggested however by some of the investigators that the effectiveness of the drug depended upon an enhanced cellular activity. Others believed that the sulfonamides were bacteriostatic and that phagocytosis was of little value. There finally came the recognition that a normal cellular defense overcame the infection only after the invading organisms were inhibited by the chemotherapy. This view has been strongly supported by the occasional case of overwhelming infection, where agranulocytosis also exists, despite intensive treatment.

One of the original hypotheses concerning the action of prontosil against experimental streptococcal infections in mice was the one advanced by Levaditi and Vaisman (173) who suggested, without much experimental evidence, that an interference with capsule formation rendered the microorganisms susceptible to phagocytosis. Domagk (77) had previously claimed that phagocytosis of the streptococci by leucocytes in mice treated with prontosil was important in clearing the tissues of the infecting organisms. In this country, Long and Bliss (177), in one of their earliest papers on the subject, claimed that when sulfanilamide was used in the treatment of beta hemolytic streptococcal infections, "phagocytosis of the streptococci by the polymorphonuclear leucocytes plays a paramount role in controlling the infection in the early stages of the treatment and that later the monocytes join in this phenomenon." Very shortly after this appeared, the same authors (27) stated that bacteriostasis was the only demonstrable factor which led to the control of *Clostridium welchii* infections in mice treated with sulfanilamide. They also interpreted in the same way the results obtained with mice experimentally infected with streptococci and treated with sulfanilamide. Long, Bliss, and Feinstein (178) subsequently reported that the drug decreased the rate of bacterial reproduction and did not enhance phagocytosis as they had previously suggested. They found no appreciable degree of phagocytosis when peritoneal exudates were examined from treated and untreated mice.

Chandler and Janeway (44) measured an increase in vitro phagocytosis in the presence of dilute solutions of sulfanilamide. They suggested that the increase was due to some non specific action of the drug. Finkelstein and Birke-land (90) confirmed the above findings and thought that the sulfonamide or a serum-sulfonamide complex acted like an opsonin. Additional in vitro experiments by Tunncliff (282) showed that prontosil soluble (the sodium salt of prontosil) diluted 1 1,000-1 1,000,000 and sulfanilamide diluted 1 100,000-1 2,000,000 in salt solution promoted phagocytosis of *Streptococcus viridans* and *Streptococcus hemolyticus*. Both appeared to stimulate the activity of the leucocytes (cf King et al (162), cited below) but not to act as opsonin. She further observed that stabilized rough cultures of the *Streptococcus viridans* were more phagocytatable than their stabilized smooth forms. In certain dilutions, the drugs promoted a smooth to rough change in the microorganisms which made them more easily phagocytosed. Tunncliff (283) subsequently reported that sulfapyridine, diluted 1 1000 to 1 100,000 in salt solution promoted the phagocytosis of *Streptococcus viridans*, *Staphylococcus aureus* and non-capsulated *Diplococcus pneumoniae*. The leucocytes were again found to have greater activity if serum was also present but the drug did not act as an opsonin. A smooth to rough transformation was induced in all organisms grown in 1 1000 dilutions of sulfapyridine which rendered them more phagocytatable. Smears from the peritoneal cavity of mice injected with staphylococci with and without sulfapyridine indicated that staphylococci are phagocytosed beginning one hour after receiving the drug. King et al (162) had previously measured the maximal width of the migration zone of granular leucocytes of rabbit's blood grown in tissue cultures containing 1 1000 dilutions of sulfanilamide. There was a wider zone in the presence of the drug as compared with that of the controls. Haag (123) obtained an enhancement of phagocytosis of bacteria in the presence of either prontosil or para-amino benzoic acid. He emphasized the need for additional experimentation to clarify the results. As part of a series of studies on stored blood Czekalowski (56) used a rough strain of *Streptococcus viridans* and obtained a phagocytic index and percent of leucocytes active that were both increased by sulfapyridine in concentrations from 33.3 mg per liter to 0.33 mg per liter and by albucid soluble (also called sulamyd para amino benzene sulfonacetamide) in concentrations from 6.66 to 0.22 mg per liter. The maximal effect was obtained with sulfapyridine at a concentration of 6.66 mg per liter when the phagocytic index increased by 44.9% and the percent of active leucocytes by 111%. With albucid soluble the optimum concentration was 3.33 mg per liter with the index increased by 97% and percent active cells by 106%. Both drugs decreased phagocytosis in relatively high concentrations and the inhibitory effect could not be explained as a pH change. The enhancement of phagocytosis by these sulfonamides was interpreted as due to a stimulating effect on the leucocytes rather than to an opsonizing action. Reed and Orr (237) on the other hand reported that the leucocytes in the blood phagocytosed *Staphylococcus aureus* at a normal rate in the presence of sulfanilamide or one of four of its derivatives in concentrations ranging from 8-80 mg per 100 cc. The leucocytes in the body cavity of mice infected with *Clostridium welchii*

ingested the bacteria more rapidly when treated with large doses of one of the sulfonamides than was the case for untreated animals. They also found that more phagocytosis occurred in wounds infected with *Cl welchii* or *Cl sordellae* and treated locally with sulfathiazole than occurred in untreated wounds. While Mellon and McKinney (199) believed that the sulfonamides induced a phase transformation in bacteria which rendered them more easily ingested by the phagocytes, Reid (238) could detect no change in the capsules of *D. pneumoniae* in the presence of sulfapyridine in vivo or in vitro, nor could he obtain an increase in phagocytosis of pneumococci in vivo or in vitro as a result of the drug's action. He did conclude, however, that normal phagocytosis of the growth-inhibited bacteria was responsible for overcoming the infection. McIntosh and Whitby (190) were also unable to stimulate an increase in phagocytic activity of leucocytes with sulfanilamide, and Osgood and Brownlee (224) found that the drug had no direct effect upon phagocytosis when tested on tissue cultures of human bone marrow. In contrast to the results of Tunnick (282) (283) and King et al (162), Coman (49) obtained no chemotropic response to prontosil by leucocytes and found that sulfanilamide stopped all movement in the concentrations he tested. The effect of six widely used sulfonamides on phagocytosis by human leucocytes was tested in vitro by Gershenfeld and Silver (101). Sulfanilamide, sulfathiazole and sulfadiazine caused slight increases in the total number of leucocytes showing phagocytosis and a variable increase in the number showing moderate or marked phagocytosis. Sulfapyridine, sulfaguanidine and succinylsulfathiazole produced a slight decrease in these values.

The contradictory nature of the results in these in vitro experiments in the hands of different investigators raises more questions than are answered. If the therapeutic implications, which actually served as the impetus for undertaking the tests in most cases, are overlooked, it is difficult to understand why a sulfonamide increases the phagocytosis of some test particles and not others even when the particles appear to be the same. It is not unlikely, however, that contradictory results, in certain instances, are due to a difference in the complex chemical make-up of the test particles. But it is more likely that the procedures employed by the investigators varied sufficiently to account for the results. These data serve to emphasize the difficulties inherent in quantitative phagocytic studies. There are so many variables in the procedure that are known to be capable of invalidating experiments otherwise carefully conceived and executed that one is forced to reserve judgment as to the final value of the above results.

Dóczy and Horvath (74) (75) suggested that an increased cellular response and an enhancement of phagocytic activity following sulfonamide therapy in experimental animals and in men might be responsible for the therapeutic usefulness of the compounds. Welch, Wentworth and Mickle (298) administered sulfanilamide to animals experimentally infected with *Brucella abortus* and found an increase in the opsonocytophagic activity for the organisms. The drug appeared to act through a stimulation of the defense mechanism of the infected animals by increasing the production of specific opsonins thus affecting

a neutralization of the endotoxic or aggrassin-like substances formed by the organism. This permitted the enhanced phagocytosis. Welch (297) also observed an increase in phagocytosis in cases of human brucellosis or in guinea pigs infected with *Brucella abortus* and treated with sulfanilamide. Normal guinea pigs or humans with other diseases treated with sulfanilamide showed no change in the opsonocytophagic index for *Brucella abortus* nor did he find that the drug acted in vitro to elevate phagocytosis. In infected guinea pigs treated with the sulfonamide the phagocytic index might be elevated even when no drug was present in the blood stream. The serum of such animals was capable of increasing the ingestion of the bacteria when mixed with normal guinea pig or human leucocytes. He attributed this action to an indirect effect of the drug in increasing the opsonic power of the blood only in the presence of the organism. Moreover, this property of the serum was destroyed by the addition of small amounts of a concentrated filtrate of a *B. abortus* culture. Wood (311) compared the action of antipneumococcal serum with that of sulfapyridine in experimental *D. pneumoniae pneumonia*. The serum acts immediately and stops the spread of the pneumonic lesion by immobilizing the invading organisms through agglutination and the drug accomplishes the same result more slowly through bacteriostasis. In both cases the final destruction of the pneumococci depends upon phagocytosis, but in the animals treated with sulfapyridine this apparently occurs in the absence of circulating type specific antibodies. Prior to Wood's experiments, Cooper and Gross (51) observed infrequent phagocytosis in all smears and sections from both sulfanilamide-treated and untreated rats with experimental pneumococcal pneumonia, with no difference in the frequency in the two groups. Fleming (91) found that the blood of patients treated with sulfanilamide against *Strept. hemolyticus* or *D. pneumoniae* infections had enhanced antibacterial properties but no change in the efficiency of the leucocytes. Goldstein and Graef (105) successfully treated experimental pneumococcal pneumonia in rats with either sulfanilamide or sulfapyridine but concluded that the disposal of bacteria did not appear to be related to phagocytosis. A similar conclusion was reached by Mellon, Gross and Cooper (198) in mice infected with *Streptococcus hemolyticus*. Gross, Cooper and Peebles (120) successfully treated splenectomized mice infected with the same organism and found that the sulfanilamide was just as effective in these animals as in normal controls.

The macrophage response in sulfanilamide-treated mice with hemolytic streptococcal peritonitis was studied by McKinney and Mellon (191). While some strains of bacteria were phagocytosed by neutrophils, others seemed to require the presence of macrophages for their disposal. Gay and Clark (97) observed the mode of action of sulfanilamide in experimental streptococcus empyema and felt that locally derived clasmatocytes were required in complete sterilization of the treated animals. They believed that the bacteriostasis produced by the drug served to protect the accumulated leucocytes and to allow the natural defense macrophages to accumulate. Lushbaugh and Cannon (185) treated the pneumococcal dermal lesions of rabbits with sulfapyridine and

presumed that the drug acted upon the bacterial cell body rather than the capsule. Under these conditions, they found no evidence that phagocytosis played as conspicuous a role in disposing of the pneumococci as it did in acquired immunity.

Harris and Miller (132), in a very ingenious experiment, introduced large numbers of *Streptococcus hemolyticus* contained in collodion sacs into the peritoneal cavity of rabbits treated subcutaneously with sulfanilamide. The bacteria were killed in the absence of phagocytosis and frequently in the absence of precipitable protein. These results would seem to prove that phagocytosis is not essential in the mechanism of action of the drug in vivo even though it may normally play a complementary role.

Nordenson and Heidenstrom (215) tested the action of sulfapyridine on the intravital phagocytosis of Chinese ink by bone marrow. In certain cases there was an increase in the activity of the myeloid cells but not of the reticulo-endothelial cells. Their results permit no conclusions, however, as to the increase in phagocytosis of bacteria even though there is the suggestion of a general increase in phagocytosis within the body. However, the number of cases was too small and too variable to permit any generalizations.

Zernoff and Gorbacheff (322) injected sulfanilamide into caterpillars experimentally infected with comparatively large doses of *Staph aureus*. Phagocytosis was accelerated and the injected bacteria disappeared in 2-3 hours. Unmedicated controls had staphylococci in the blood 48 hours after being inoculated.

b Gastric mucin. Nungester, Wolf and Jourdonais (216) first demonstrated that the virulence of bacteria injected intraperitoneally into mice is increased in the presence of gastric mucin. The mucin could be introduced from 5 to 6 hours before the organisms and the defensive mechanism of the host was still inhibited. Miller and Castles (204) confirmed these findings using as few as ten organisms of the most virulent strains of *Neisseria intracellularis*. They observed very little phagocytosis and concluded that the increased invasiveness of the bacteria was due to a local interference with the defense mechanism of the mice. Nungester, Jourdonais and Wolf (217) reported that gastric mucin enhances the virulence of organisms injected subcutaneously and intratracheally as well as intraperitoneally. They believed that the mucin did not inhibit phagocytosis (see below) but reduced the bactericidal properties of the phagocytic cells. Anderson and Oag (6) verified the above observations for *N intracellularis*, *Staphylococcus aureus* and certain strains of *Streptococcus hemolyticus*, but found no change in the virulence of *Streptococcus viridans*, *E typhi*, *E coli*, and "*B anthracoides*". The gastric mucin was chemically fractionated with the result that only the protein moiety was capable of increasing the virulence of *N intracellularis*. Ørskov (221) concluded that the greater pathogenicity of bacteria injected into the peritoneum of experimental animals was due to the prevention of extracellular lysis and an inhibition of phagocytosis. Tunnick (284) also found that gastric or salivary mucin inhibited phagocytosis.

of bacteria by forming a covering over the cell which prevented vital staining. In vivo experiments revealed that mucin-coated staphylococci were not ingested by leucocytes for 2 hours following injection while in control mice phagocytosis was observed after 1 hour. In the former case the animals died within 24 hours and in the latter they recovered.

c. Natural and artificial opsonization (1) In vitro experiments. The action of normal non-immune serum in promoting phagocytosis has long been recognized (210). An elucidation of the role played by complement in this process has been the object of several investigations. Gordon, Whitehead and Wormald (115) inactivated the 4th component of complement in serum by means of ammonia and found that this serum had lost none of its opsonic activity for *Staph aureus*. The same authors (116) incubated normal serum at 37°C for 2 hours with this organism present in amounts sufficient to remove the opsonic complement activity but the 4th component was not removed. Gordon (113) then demonstrated that congo red which prevented the bactericidal and hemolytic activity of normal serum (complement) was still capable of exerting its opsonic activity. Gordon and Thompson (117) subsequently reported three additional ways in which complement could be inactivated without the loss of the opsonizing power of the serum. These were (a) long standing of the serum at room temperature (b) the addition of acid or alkali and (c) the action of hypertonic concentrations of certain sodium and potassium salts. In trying to account for the experimental facts, two possible explanations for the relationship between complement and opsonin were favored. First, complement may act as an opsonin, when present in its complete form, but when it is modified or altered in structure by various agencies, the modified complement may still act as an opsonin provided it has not been too drastically modified. This would demand that opsonization is still possible with wider divergence from the optimum state than is permissible for complement action. And second, opsonin and complement are different systems acting independently but showing considerable resemblances to one another in some respects. The latter view was favored by Gordon and Thompson but observations by other investigators support the former concept. Delves (68) used purified serum protein antigens and found that the removal of a precipitin by absorption with the homologous antigen also completely removed the agglutinins and opsonins. The complement fixing power of the albumin antiserum was completely removed and it was greatly lowered in pseudoglobulin antiserum after absorption. These results indirectly suggest that complement may be necessary for phagocytosis. Castelli (40) confirmed the findings of Delves when he showed that depriving an agglutinating serum of its agglutinins by absorption with the specific bacteria, totally deprived the serum of its phagocytosis promoting properties. In contrast to Gordon's results, however, Castelli found that serum treated with Congo red not only lost its complement but also its ability to enhance phagocytosis. He concluded that opsonins were inseparable from complement and bacteriotropins were inseparable from agglutinins. Recent attempts have been made by Maaloe

(187) and by Ecker and Lopez-Castro (81) to analyze the factors responsible for the opsonic activity of fresh sera so as to make the determinations more quantitative. Maaloe concluded that the same C'^* was the active factor in phagocytosis as it was in hemolysis, that calcium ion was essential and that C'_4 was likewise needed, contrary to the belief of Gordon, Whitehead and Wormall (see above). It was also concluded by Ecker and Lopez-Castro that C'_4 was needed for opsonization but that sera, from which C'_3 had been removed, showed little or no loss of opsonic activity. Additional experimental evidence, however, offered as support for the conclusions of Gordon and Thompson was presented by Gordon (114). Opsonin was taken up from ammonia-treated serum by *Staphylococcus aureus* in such a way that it could not be removed from the bacteria by thorough washing. Sensitized blood cells, on the other hand, were unable to retain the material absorbed from the serum after washing, in such a state that the addition of the 4th component of complement brought about hemolysis. The interpretation that opsonin was not therefore a defective or incomplete complement seemed to be open to question in the light of the more recent work.

The action of tannin in promoting phagocytosis was originally described by Freund (93), by Reiner and his colleagues (239) (240) and others. These observations were offered in support of the concept that the ingestion of particulate matter by cells depends upon the free surface energy relationships mentioned in an earlier section of this paper. Additional experiments, now available, are most readily explained on this basis. A large group of substances, including many vegetable tannins, salts of chromium, iron, aluminum, lead, zinc, copper, magnesium, calcium, barium, cadmium, nickel and cobalt, and also gallic, acetic, lactic, sulphuric and picric acids, formaldehyde and catechin were tested for opsonic action against *Staphylococcus aureus* by Gordon and Thompson (118). A definite parallelism was found between tanning action and opsonic activity. The irreversible chemical changes characteristic of tanning were believed responsible for the changes in physical properties which made phagocytosis possible. Even though dehydration is an invariable consequence of tanning action, it was not considered to be the primary factor. Those substances possessing opsonic activity almost always exhibited agglutinating power. This would be predicted on the basis of the theory. The same authors (119) extended their experiments to studies with *E. typhi*. Essentially the same results, with some minor differences, were found.

Fethke (86) tested the effect of salts of normal saturated fatty acids on phagocytosis *in vitro*. The lower homologs of C_1 to C_6 acids produced no change in phagocytosis while the salts of C_6 to C_{10} acids markedly increased the activity. Acids with longer carbon chains had a toxic and inhibitory effect which was not due to changes in pH. Potassium salts of dibasic fatty acids (87) were

* Reviews by Pillemer (234) and by Heidelberger and Mayer (134) may be consulted for an account of the chemistry of complement and a characterization of its various components.

toxic starting with the C_{13} compound and reaching a point of complete inhibition of phagocytosis by a 1:50,000 dilution of the C_{13} acid. None of these increased phagocytosis.

Hoder (142) exposed *Staphylococcus aureus* to the action of bacteriophage and even those that were bacteriophage fast were engulfed more readily than control bacteria. Similar findings were recorded for other species of bacteria. Earlier workers (210) reported the same effect which is apparently due to changes induced in the bacterial surface.

Hammond and Weinmann (126) established the presence of a phagocytosis-stimulating factor in the saliva of 41 patients selected at random. It was identified as opsonin on the basis of absorption and heating experiments. The same authors (127) then compared the phagocytosis in saliva from 18 caries-free individuals with that from 10 cases of rampant caries. With saliva from the former group an average of 37% of the leucocytes ingested bacteria while saliva from the persons with caries stimulated an average of 4% of the leucocytes. When both saliva and serum were used in the tests a slight inhibition was noted with saliva from caries-free subjects but it was marked when saliva from persons with rampant caries was used. This would seem to be in part a dilution effect.

Sugiyama and Takigawa (274) tested the simultaneous uptake of both vital dyes and carbon particles by leucocytes and concluded that the specific activity of the cell surface necessary for phagocytosis was not identical with the phenomenon of supravital staining since dyes were taken up by dead cells and carbon entered only living cells.

(2) *In vivo* experiments. The experiments to be reviewed in this section are primarily qualitative and constitute an approach to phagocytosis that in many cases could be made quantitative by use of the technique of Maxfield and Mortensen (196). For example, avertin (tribromoethanol) anaesthesia, according to Aoki (11), impaired the phagocytosis of *Staph. aureus* by guinea pig leucocytes when the dose was large enough to cause respiratory difficulty or cardiac disturbances. Vilardo (288), on the other hand, reported that subcutaneous injections of novocain into rabbits increased the phagocytic potency of the leucocytes toward 24 hour cultures of *Staph. aureus*. Egoroff and Lapteva-Popova (82) found that acidosis produced by injections of NH_4Cl lowered the ability of the reticulo endothelial system to take up Congo red and depressed the phagocytic potency of neutrophils and monocytes. The simultaneous administration of hydrolytic products of animal organs, containing principally polypeptides and amino acids, and NH_4Cl , resulted in an acidosis which increased the Congo red index and strengthened the phagocytic ability of neutrophils and monocytes. Their untreated control animals had indices that were constant for 16 days. Wasizu and Simizu (291) observed the effect on phagocytosis of the pH of India ink injected into experimental animals. Optimum ingestion occurred between pH 6-8, especially around pH 7.4. Values below 6 and above 8 were unfavorable for phagocytosis. Czekałowski (56) tested the action of pH on

the leucocytes of stored blood ingesting *Streptococcus viridans*. No definite effect was observed between pH 6.2 and 9.05. At pH values near 9 and with long incubation periods, there was a slight tendency for phagocytosis to increase.

Intravenous injections of electro-colloidal copper selectively paralyzed the reticulo-endothelial system, in experiments carried out by Jancsó and Jancsó (152). Germanin (the sodium salt of a complex aromatic aminosulfonic acid carbamide, also known as suramin sodium), however, caused a marked increase in the phagocytosis of trypanosomes in infected animals. Since the withdrawal of sugar from the animals had the same effect by rendering the trypanosomes motionless and thereby susceptible to ingestion, it was thought that germanin might inhibit the sugar metabolism of the parasites. Dóczy (72) (73) found that injections of 2 to 3 mg of metallic bismuth, in the form of an oil-soluble salt, per kilo body weight into rabbits produced an increase, of several days duration, in the phagocytic power of the blood cells. This was tested with suspensions of *Staphylococcus aureus* and it was suggested that the therapeutic value of bismuth compounds depended upon this enhancement of the cellular defense as well as upon the disinfectant action. Dóczy and Horvath (76) effectively treated rabbits and guinea pigs experimentally infected with *Streptococcus hemolyticus* or *Staphylococcus aureus* with ulron (dimethyl disulfanilamide). The phagocytic activity of the reticulo-endothelial system was depressed when a 1% Congo red solution was also administered as compared to the activity found with ulron alone.

The action of heparin in controlling experimental *Streptococcus hemolyticus* infections in rabbits was investigated by Magerl (192). The treated animals survived while the controls died. It was shown that the phagocytic activity of the leucocytes was markedly stimulated and the autolytic digestion of the absorbed bacteria was more rapid in animals receiving heparin than in untreated controls. Heparin injections in guinea pigs exerted an unmistakable enhancing effect on phagocytosis. The author concluded that this anticoagulant was capable of promoting phagocytosis. Rigdon and Schrantz (246), on the other hand, could detect no difference in the amount of carbon taken up by cells of the reticulo-endothelium in normal rabbits and those given 20 mgm of heparin intravenously. Five cc of a 5% saline solution of Higgin's India ink was injected by the same route 5 minutes following the heparin and the animals were sacrificed 30 minutes later. This quantity of heparin should be sufficient to affect phagocytosis since the blood of the treated rabbits failed to clot completely for a period of 18 hours. Rigdon and Wilson (245) had previously detected no effect of intravenous injections of heparin on the localization of neutrophils in areas of injury in rabbits. Heparin also failed to affect the development of an acute inflammatory reaction in the skin. More recently, Rigdon (244) obtained no evidence that heparin inhibited the phagocytosis of malarial parasites. These results are in agreement with those of Boerner and Mudd (previously referred to in sec. 1) who advocated the use of heparin as the best anticoagulant for quantitative in vitro measurements of phagocytic activity.

Kelson and White (159) described a new method of treating subacute bacterial

endocarditis in which a combination of sulfapyridine and heparin were employed. The rationale behind this therapy was based upon the earlier demonstration by Kinsella (163) that the blood of patients with this disease usually had a high titer of antibodies for the organism (frequently a strain of *Strept viridans* but many other bacteria may be responsible for the infection). Despite this fact, Friedman, Katz and Howell (91) showed that the microorganisms responsible would grow in the serum but were quickly destroyed, even in normal serum, when white blood cells were present. Thus phagocytic uptake by the leucocytes seems to be the basic means of clearing the infection. However, as Waitzman, Smith and Martin (289) have described it, the bacteria accumulate within the margin of the valve cusps and are free from attack by leucocytes arising from within the tissue since no blood vessels penetrate to this region and they are also secure from antibodies and chemotherapeutic substances in the blood bathing the valve from without. Usually the bacteria lie near the periphery of the vegetation which consists of a mass of fibrin and platelets, an ideal culture medium and protective barrier, which Duncan and Faulkner (79) have found to be absolutely impervious to the sulfonamides. Heparin was added to prevent fibrin formation, and, as Kelson and White put it, in the hope that it would "(1) restrict the nidus and culture medium for bacterial growth, (2) prevent embolism from the freeing of fresh thrombus, and (3) check the growth of the vegetations so that proliferating fibroblasts may fill in the areas thus limited." Numerous reports of clinical tests soon appeared in the literature and when penicillin became available for civilian use, Loewe, Rosenblatt, Greene and Russell (176) used this antibiotic in combination with heparin in a series of cases. Seabury (260) has reviewed the results of the different methods of treating subacute bacterial endocarditis and concludes that heparin should rarely be used due to the great risk of inducing cerebral hemorrhage. Dawson and Hunter (59) had previously come to the same conclusion. Penicillin, and possibly some of the newer antibiotics, seems to be the therapy of choice.

Klepsen and Nungester (165) found that injections of varying amounts of 15% alcohol in rats decreased the chemotactic response of polymorphonuclear leucocytes toward *D. pneumoniae*. This was also observed in human blood to which alcohol had been added. Since chronically intoxicated rats were more susceptible to pneumonia, it was suggested that the depressed leucocytic activity was responsible.

Tabusso and Silvani (275) tested the effect of carbon tetrachloride poisoning on the phagocytic values in healthy rabbits and found them to be diminished. The carbon tetrachloride was introduced through the lungs and skin.

5 Phagocytic Changes in Stored Blood

At about the time that blood banks came into general use, a knowledge of the cellular changes that accompanied the storage of blood became important. Karavanoff (157) published the results of some of the first experiments on this subject in 1935. The leucocytes were found to retain their phagocytic capacity for 4-6 days. In the case of infectious diseases requiring transfusions, he recommended that fresh blood or blood stored no more than 2 days be used. Gnoninski

(104) made no phagocytic measurements, but he did record the many rapid qualitative and quantitative changes to which leucocytes were subject during storage. For example, the neutrophils decreased from an average of 65% to 15% in 3-5 hours and then gradually increased up to 94% in 13 days.

MacDonald and Stephen (188) reported that the leucocytes of blood stored in I. H. T. solution were unable to ingest *Staph. albus* after 24 hours. Kolmer (166) tested the phagocytic activity of neutrophils of citrated human blood kept at 4°-6°C for *Staph. aureus*, *Strept. hemolyticus* and *E. coli*. Under these conditions phagocytosis was definitely reduced within 72 hours after collection, was markedly so on or about the fifth day, and was almost totally absent on or after the seventh day of preservation. This may have been due in part to deterioration of normal opsonins but was primarily due to autolytic and degenerative changes in the leucocytes. In the case of placental and retroplacental blood preserved with citrate, Kaiavanov and Baksheev (158) measured a decrease in phagocytic activity of the leucocytes during the first day of collection. There was an increase on the second day followed by a decline on the third day. Phagocytic function was lost 5-6 days after collection. Monocytes retained their activity longer than the other cells and retroplacental blood lost its phagocytic activity sooner than placental blood. Czekalowski (57) evaluated the effect of storing blood in a 3.8% solution of sodium citrate on its phagocytic power against *Streptococcus viridans*. On about the fourteenth day of storage, phagocytosis could not be demonstrated. The leucocytes decreased in vitality with a weakening in pseudopod formation first appearing, then motility was lost and finally the Brownian movement of cytoplasmic granules disappeared. The decrease in phagocytosis was directly proportional to the decline in leucocyte numbers and was inversely proportional to leucocyte degeneration. The leucocytes of stored blood lost their phagocytic ability against bacteria opsonized by stored plasma on the fifth to eighth day but when fresh plasma was used to opsonize the bacteria, it was not lost until the eleventh to fourteenth day. Thus the normal opsonin declined, but since the addition of a small amount of fresh plasma increased the opsonizing activity of stored plasma, complement, or one of its components, seemed also to disappear. On the basis of these results, the author recommended that blood stored longer than 24 hours, or 48 hours at the most, should not be used in transfusions with the object of strengthening the recipient's defense against infections. In a more recent report, Czekalowski (58) has extended the above findings with *Strept. viridans* to other bacteria, including *E. coli*, *Proteus vulgaris*, *Strept. faecalis*, *Strept. hemolyticus*, *Staph. aureus*, and *Staph. albus*. The medium in which *Strept. hemolyticus* and *Staph. aureus* were grown was shown to contain a factor capable of inhibiting the phagocytic activity of leucocytes, eliminating the weaker cells and decreasing the average number of bacteria engulfed. Fresh leucocytes were inhibited slightly if at all by these substances. The tendency of leucocytes for spontaneous phagocytosis ceased during the first day of storage. The opsonizing action of the plasma was also reinvestigated and two kinds of opsonins were shown. One was designated as the thermostable "residual phagocytic factor" and the other,

almost five times as strong, required for its activity a factor inactivated by both heat and storage of the plasma. It is this last factor that was replenished by the addition of small amounts of fresh plasma in regenerating the opsonizing power of stored blood. Heat-inactivated plasma could not be restored in this way. The "residual phagocytic factor" possessed no selective activity but was responsible for the "basic" opsonization of various species of bacteria.

6 The Role of Nutrition in Phagocytic Activity of Tissues

The importance of nutrition in resistance to infection has recently been reviewed by Schneider (258). There is an enormous literature on the subject but much of it is so contradictory that the familiar linkage between famine and pestilence is, as Schneider puts it, "made conspicuous more by reiteration than by demonstration." In even the restricted part of the whole problem which will be dealt with here, there is no uniformity of results. It is, moreover, impossible in most cases for the reviewer to pick out the divergence in procedure or in technique that might account for data obtained in what appear to be essentially identical experiments but lead to opposite conclusions. Here again, the complexity of this type of investigation is emphasized along with the need for more critical detailed analyses of the subject.

Findlay and Mackenzie (88) and Werkman (306) were unable to detect any change in phagocytosis *in vitro* in vitamin A or B complex deficient animals. Rats were used as experimental animals and Werkman also studied rabbits. Gellhorn and Dunn (98), however, found that the serum of vitamin A deficient rats might increase or decrease the normal phagocytic index. The increase preceded the decrease which came only after prolonged deficiency. These findings were explained as the consequence of a rise or fall in antibody production elicited by infectious processes which accompany the deficiency disease. Since the antibody production could not keep pace with the demands of the organism, the phagocytic index fell. In some cases, a fully developed vitamin A deficiency was accompanied by an increased phagocytic activity so that this vitamin was not indispensable for antibody production, but with further progress of the disease, the decline in phagocytosis was observed. The authors used this as an explanation for the fact that the vitamin A deficient rat was more susceptible to infections than animals fed normal diets but they offered no experimental proof that such was the case. They were unable to correlate weight loss or severity of deficiency symptoms with the changes in phagocytosis. The changes were shown to be completely reversible when the diet was returned to normal for a sufficiently long time. In a later publication, Gellhorn and Dunn (99) evaluated the phagocytosis-promoting power of sera from rats in different stages of malnutrition. In acute starvation, the decrease in phagocytic index could be correlated with body weight loss. The increased phagocytic activity observed in some of these animals was attributed to the presence of acute infections. With chronic undernutrition, the phagocytic index also decreased when loss in body weight was greater than 38%. The authors suggested that this may have been due to a vitamin A deficiency, rather than to loss in body weight.

Experiments to evaluate the effect of vitamin A deficiency in rats on the in

vivo phagocytosis by the reticulo-endothelial system were carried out by Gaál and Szabó (95). The ingestion of India ink was decidedly decreased in the deficient animals compared to the controls. It was also seen that the size of ink particles ingested was larger in the controls. This functional disturbance was more pronounced in vitamin A than in vitamin B deficient animals. Lawler (171) suggested that the greater susceptibility of vitamin A deficient rats to *Strongyloides* infection could be traced to some impairment in the activity of the reticulo-endothelial system. Wright (320) came to the same conclusion in his work on the relation of vitamin A deficiency to ascariasis in the dog but added that the granulocytes also had a lowered capacity. Rose and Rose (250) obtained indirect evidence that vitamin B (complex) deficient dogs might have a less active reticulo-endothelial system since *Staph aureus*, artificially introduced, survived longer in the blood stream of these animals than in isocaloric controls.

Messina and Verga (202) tested the in vitro phagocytic activity of the blood of rabbits treated with vitamin C. There was an increase in this function, as compared to normal animals, which was attributed to an elevation in the opsonizing power of the plasma. Statistical analysis of the data was not attempted. Naccari (212) also obtained an increase in the phagocytic activity of the blood of rabbits treated for six consecutive days with 50 mg of ascorbic acid daily. There was no change, however, in the bactericidal potency of the blood against several species of bacteria. Tonutti and Matzner (279) found that phagocytic cells were loaded with vitamin C which they considered essential for the digestion of ingested material. They then made the rather startling conclusion that vitamin C deficiency in pneumonia results from increased phagocytosis. A single experimental observation is used as the basis for a sweeping generalization in this case. Naraci (213) frequently obtained a parallel decline in phagocytic ability of the blood and the blood ascorbic acid level in the course of measles. Correlation between the two facts was implied.

Following the observations by Mills and Schmidt (205) which showed that mice kept in a warm humid environment were more susceptible to experimental Diplo pneumoniae type I infection than mice in a cool environment, Cottingham and Mills (52) studied the effect of environmental temperatures and vitamin deficiencies upon phagocytic functions in rats. A single deficiency in thiamin, riboflavin, pyridoxine, pantothenic acid, choline, or ascorbic acid severe enough to retard growth produced a reduction in phagocytic activity. The highest phagocytic function seemed to occur at levels of vitamin intake that exceeded the need for good growth. These results have been questioned (218) (131) because of the small number of leucocytes examined in evaluating phagocytosis, but Mills and Cottingham (207) have defended the reliability of the data. Mills and Cottingham (206) found a relationship between protein consumption and phagocytosis. The blood leucocytes of rats kept in an environment of 68°F had an optimum activity with 18% dietary protein while the activity increased to the highest protein level (36%) used in the study in tropical heat. The time required for the phagocytes to undergo a change in activity from one level to another as the nutritive status was altered from adequate to inadequate, or vice

versa, was determined by Cottingham and Mills (53). Rats lost weight during the first week on a deficient diet but the blood phagocytes did not become less active until the second week and the lowest level of phagocytosis was reached at the end of the fourth week. The converse of this was found in the blood of rats changed from a deficient to an adequate diet in the recovery of phagocytic activity. A similar lag in the decline of phagocytosis during the remission of blood loss anemia was observed by Berry and Haller (21) (see below). In the same publication, Cottingham and Mills reported a diminished phagocytic activity of leucocytes in malnourished humans. Dietary correction and vitamin supplementation resulted in phagocytic improvement, which, on the average, increased linearly from the third week onward, reaching normal levels in about five weeks.

TABLE II
Phagocytic Activity of Male Rats on Different Diets
from Berry, Davis and Spies (17)

GROUP	DIET	MEAN NUMBER OF BACTERIA PHAGOCY- TOSED PER PMN	DIFFERENCE OF MEANS FROM BASAL GROUP	PROBABLE ER- ROR OF DIFF- ERENCE $\times 4$
1	Basal*	8.94 \pm 0.36		
2	Basal + casein**	8.27 \pm 0.37	0.67	2.06
3	Basal + casein + minerals***	7.89 \pm 0.35	1.05	2.00
4	Basal + casein + B vitamins†	11.94 \pm 0.39	3.00	2.10
5	Basal + casein + minerals + vita- mins	11.74 \pm 0.42	5.80	2.21

* Basal diet 35.6% corn meal, 28.1% enriched white flour, 17.6% pork fat, 18.7% cane sugar

** 18% casein

*** 4% salt mixture

† Thiamin, riboflavin, pyridoxine, inositol (all 0.2 mg per rat per day), Ca pantothenate 10 mg, nicotinamide 25 mg, and choline 200 mg

In a number of unpublished observations by Berry, Davis and Spies the phagocytic activity of neutrophils from patients with mixed dietary deficiencies was found to be lower than that of healthy controls. The mean number of bacteria ingested by 100 leucocytes in the blood from these patients was frequently 50% or more below the control values. In rats fed a grossly deficient diet, patterned after that consumed by many families in the region of endemic malnutrition in Alabama, Berry, Davis and Spies (17) measured a decrease in the phagocytic activity of neutrophils as compared to that in animals on an adequate diet. Data are shown in Table II. There was a deficiency in most of the vitamins of the B complex in the first three groups and in protein in only group one. Wissler focused his attention on the effects of protein depletion upon the response of rabbits (309) and of male albino rats (310) to pneumococcal infection. There was a lowered granulocytic response in the early stages of infection in the malnourished rabbits and a negligible amount of phagocytosis in dermal lesions resulting from the deficient diet. White rats were also found to have an impaired

phagocytic function but immunization of the animals was followed by an increased phagocytic activity. An impaired leucopoiesis was also believed to be related to the decrease in resistance to pneumonia in the depleted animals. In contrast with the above results, Guggenheim and Buechler (122) found that the phagocytic activity of the peritoneal fluid in rats suffering from various forms of nutritional deficiency was not changed. In addition, the bactericidal properties of the fluid were evaluated and in each case the determinations were made following injections of *Salmonella typhimurium*. Deficiency of either thiamin, riboflavin or vitamin A resulted in lowered bactericidal power but the phagocytic function remained unimpaired. In fact, an increase in phagocytosis accompanied a prolonged moderate or sudden severe restriction of food intake but the bactericidal action of the peritoneal fluid was diminished. Even protein supplementation of such a low caloric diet failed to correct the observed changes. No mention was made of phagocytic studies with blood leucocytes under the conditions of these experiments nor were quantitative *in vitro* tests with the exudative leucocytes performed.

Colombo (48) noted a moderate increase in complement accompanying malnutrition in children. The phagocytic titers were frequently elevated. Riddle, Spies and Hudson (243), on the other hand, found a low complement titer in very ill acutely deficient patients and a slightly subnormal or normal titer in subclinical or mild cases. Bieler, Ecker and Spies (25) studied the serum proteins in eight cases of hypoproteinemia due to nutritional deficiency and reported that no significant variation from normal values in complement titers or in opsonic indices were observed. All of the cases were also anemic but were selected so that none was infected. Normal opsonization was also observed by Berry, Leyendecker and Spies (20) in their studies on the phagocytic activity of anemic blood.

7 Other Factors Modifying Phagocytosis

a Nervous stimulation. Ludány, Buta, and Gyory (180) claimed that asphyxia, by stimulating the sympathetic nervous system, increased the ability of serum to promote phagocytosis. This effect lasted for 30–75 minutes after the animals were restored to normal. A 6–15% increase in phagocytosis was reported by Golodets and Pushkov (107) when the perfusate of an isolated frog's leg, collected during stimulation of the sympathetic nervous system with an induction coil, was added to a suspension of leucocytes in Ringer's solution. An increase of this magnitude would demand a rigid statistical analysis. Golodets (106) also stated that stimulation of the sympathetic nervous system increased phagocytosis and that acetylcholine in a dilution of 1:100,000 had a similar effect on the process.

b Endocrines. A more extensive treatment may be found in Mudd, McCutcheon and Lucké (210). Parodi (226) compared the ability of leucocytes from eleven normal dogs and eight hypophysectomized dogs to ingest powdered starch. An average of 47% of the granulocytes were active in the former group and 24% were active in the latter. Intraperitoneal injections of an alkaline extract of the anterior lobe of the pituitary gland increased phagocytosis to

normal values in the experimental dogs. The elevation began the second day after treatment and diminished somewhat after six days. The action was not specific because an extract of muscle produced the same effect. Intravenous administration of the pituitary extract did not modify phagocytosis and neither did the nasal insufflation of a ketone dried anterior pituitary powder. Thyroid powder given by mouth raised the phagocytic count. The physiological significance of these experiments is obscure. Wetzler-Ligeti and Wiesner (307) employed the rate of removal of Congo red from the blood stream in an effort to evaluate the influence of several anterior pituitary extracts on macrophagic function. Certain extracts increased this activity and on the strength of these observations a special reticulo-endothelial stimulating factor in the pituitary was postulated. This hardly seems likely in view of the recent work of Gordon (109) Gordon and Katsh (110, 111, 112). These workers, using adult male rats, investigated the phagocytic capacity of the reticulo-endothelial cells against thorium dioxide in adrenalectomized and hypophysectomized animals. A significant decrease in the uptake of thorium by the spleen was observed in the former group of rats while no change was found in the quantity of thorium in the spleens of animals from the latter group. The administration of large quantities of whole adrenal cortical extract, but not desoxycorticosterone acetate, approximately doubled the amount of thorium in the spleens of treated adrenalectomized rats when compared with that in the spleens of untreated controls, but it was less than that found in the spleens of normal control rats. Thus, the spleens from normal control animals contained 79.12 ± 7.1 mg of thorium per gram dried spleen, from untreated adrenalectomized animals 25.42 ± 2.5 mg, from adrenalectomized rats treated with desoxycorticosterone acetate 21.50 ± 2.5 mg, and from adrenalectomized rats treated with adrenal cortical extract 47.07 ± 5.9 mg. Similarly, the administration of large amounts of adrenal cortical extract to hypophysectomized animals was accompanied by a marked increase in the deposition of the thorium in the spleen. In this case, nearly three and one-half times more metal was taken up by the spleens of these animals than was found in those for both normal controls and in untreated hypophysectomized controls. It was also observed that chronic starvation, induced in normal animals, resulted in a greatly increased uptake of thorium by splenic tissue. The conclusion that the adrenal cortex exerts a regulatory influence on the functional activity of the macrophagic cells seems justified and the hypophysis, if involved at all, must act indirectly through the adrenotropic principle. These results confirm and extend those of Reiss and Gothe (241) who reported an increase in the uptake of lithium carmine in the Kupffer cells of rats following injections of adrenocorticotrophin.

Richardson (242) determined the phagocytic power of the leucocytes of diabetic patients, of depancreatized cats and of normal controls. Phagocytosis did not differ from normal in any case when the blood sugar level and alkaline reserve were within the limits commonly found in this condition. However, in both diabetic patients and depancreatized cats with acidosis or uncontrolled diabetes a significant decrease occurred in the phagocytic power of the blood

An increased phagocytic activity which occurred in normal controls following typhoid vaccine did not occur in the diabetic patients. Normal phagocytic activity in blood leucocytes also was found by Berry, Davis and Spies (19) in a small series of diabetic patients under treatment.

c Leukemia. The most extensive study of the phagocytic ability of the circulating leucocytes in various types of leukemia was carried out by Strumia and Boerner (272). Lymphocytic cells, including the lymphoid hemocytoblasts (lymphoblasts), never showed any phagocytosis. In the granulocytic series, the immature cells such as the myeloblasts and promyelocytes showed a slight but increasing phagocytic ability as they became more mature. The first granulocytic cells to show the characteristically staining granulations (the promyelocytes) were also the first cells to show definite phagocytic activity in all experiments. There is a great increase in phagocytosis accompanying the complete maturation of the cytoplasm, characteristic of the myelocyte, with an additional enhancement of phagocytosis occurring in the other granulocytic type of cells, namely, the metamyelocytes, cells with rod nuclei, and the polymorphonuclear cells. The relationship between the area of cytoplasm and the power of the cells to ingest particles was determined for myelocytes, metamyelocytes, rod nuclears and polymorphonuclears but a parallelism existed between only the last two. The difference in this case was quite small and, since the rod nuclear is the youngest cell normally present in the peripheral circulation it was concluded that no difference exists in the phagocytic activity of these and the more mature cells (neutrophils) in the blood. This conclusion has been substantiated in numerous measurements by the authors (19). Eosinophiles were found to be phagocytically active but to a lesser degree than either neutrophils or monocytes. While a fair percentage of the eosinophiles may be active each cell usually contained fewer bacteria than the other cell types. A similar conclusion was reached by Boerner and Mudd (28) in their study of a patient with eosinophilia and has been confirmed in unpublished observations by the authors. While basophiles are weakly phagocytic, the monocytic cells, the blood histiocytes, monoblasts, and monocytes, constantly show activity. These cells ingested bacteria less readily than neutrophils but they were more phagocytic against collodion granules and carbon particles.

Teng and Chung (278), using two cases of myelogenous leukemia as a source of blood, confirmed the results of Strumia and Boerner for type I pneumococci and Strept hemolyticus. Leishman-Donovan bodies were engulfed by neutrophils beyond the myeloblastic stage and occasionally by eosinophiles. Bonanno (30) studied the phagocytic ability of leucocytes from five cases of chronic lymphatic leukemia and one case of acute lymphatic leukemia. The blood was incubated with a strain of *Staphylococcus aureus* for 45 minutes at body temperature and he observed a reduced phagocytic power in all cases, as compared to normal blood cells. Tanahe (277) also reported results essentially in agreement with the above except that he believed the phagocytic ability of monocytes and neutrophils was weaker in leukemic blood than in normal blood. These observations coincide with those of Hirschberg (141) who further sug-

gested that the decreased resistance of leukemic individuals was due to this lowered phagocytic activity of the mature neutrophils. Ingraham and Wartman (149), interested in the chemotropism of leucocytes obtained from a patient with eosinophilic myelogenous leukemia and from one with dermatitis herpetiformis, reported that eosinophils exhibited a chemotactic reaction to bacteria as strong as that of normal neutrophils. There was a weaker attraction of the eosinophils by material from an animal parasite, *T. spiralis*, than by Witte's peptone. No phagocytic measurements were undertaken.

d Anemia. In the course of evaluating the *in vitro* phagocytic power of blood from malnourished patients Berry, Davis and Spies (18) noticed that in cases of anemia there was an elevated phagocytosis as compared to that of normal blood. Regardless of the type of anemia, including nutritional macrocytic anemia, pernicious anemia, iron deficiency anemia, and macrocytic normochromic anemia, an increase in neutrophilic activity was found and the magnitude of the effect was roughly proportional to the severity of the anemia, as shown in Table III. As the anemia remitted, either spontaneously or with specific therapy, the phagocytic activity fell toward normal and even below in those cases where malnutrition was also present. This may be seen in figures 1 and 2. In a series of experiments conducted by Berry, Leyendecker and Spies (20), in an effort to ascertain the source of the enhanced phagocytosis, opsonization was eliminated as the cause when it was found that normal leucocytes ingested the same average number of bacteria when they were suspended in normal serum as in serum from anemic patients. Leucocytes from anemic blood, on the other hand, were just as active in normal serum as they were in homologous serum. These results, given in Table IV, permitted the conclusion that the neutrophils from anemic blood had undergone some fundamental change which could not be correlated with greater motility but which endowed them with greater phagocytic capacities than normal cells. This conclusion was reached only after the phagocytic system had been adjusted in such a way that the number of cells was comparable in the *in vitro* tests with normal and anemic blood. Additional confirmation of this relationship was provided by Berry and Haller (21) in experiments with rats made anemic by blood loss. The animals were bled by cardiac puncture once weekly for eleven weeks. The blood withdrawn was used to evaluate the phagocytic activity of neutrophils and was compared to values obtained from a group of normal rats. Total blood cell counts and hemoglobin determinations were also made each week. Control animals were not bled more frequently than once every six weeks. By the end of this period, phagocytosis was about 40% higher in the bled group than in the control animals but there was no evidence of anemia developing under these conditions since hematopoiesis kept pace with the blood loss. The same experimental rats were then bled three times per week for five weeks resulting in the development of severe anemia and an increase in phagocytosis that was 80% above normal. Macrophages from a peritoneal exudate stimulated by the injection of mineral oil were also nearly twice as active as those from control animals at the time when the anemia was most severe. Two weeks after the

last bleeding the blood picture was normal but the phagocytic values were slightly lower than those for control animals. It was nearer normal after four weeks and essentially so after six weeks. Macrophages were phagocytically normal after four weeks. All data were treated statistically and were highly significant at the periods discussed above. As a final check on the validity of this relationship between anemia and phagocytic function, it was reasoned that

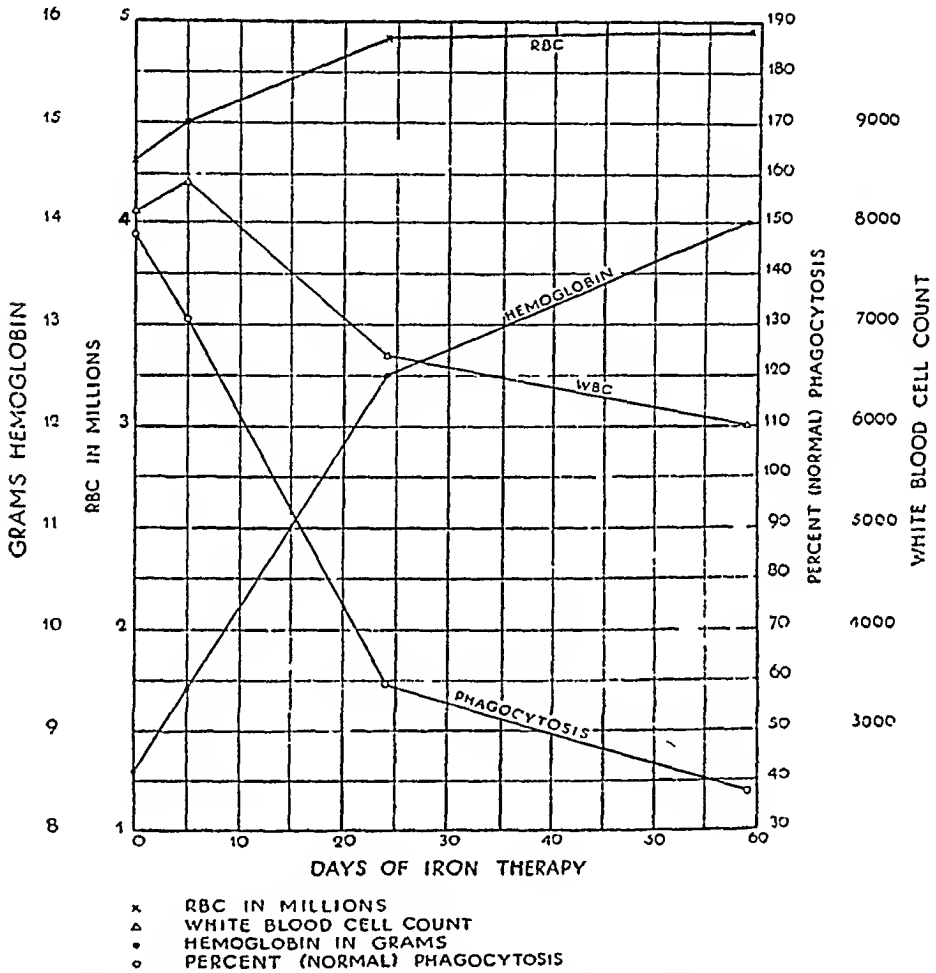


FIG 1 *—Decrease in phagocytosis with therapeutically induced remission in a patient with hypochromic anemia

animals exhibiting this increased cellular defense activity should be more resistant against bacterial infection than normal healthy control animals. In order to test this working hypothesis, Berry and Haller (22) made mice anemic by blood loss. This was accomplished by removing 2% of the body weight of each mouse in blood from the tail twice weekly for nine bleedings. At the end of this time erythrocyte totals and hemoglobin levels were approximately two-thirds of normal while the granulocytes were 61% more phagocytic than those from

* From reference (18)

normal blood. The anemic mice were then infected by intraperitoneal injection with a suspension of *Salmonella typhimurium* and their survival was compared with that of normal mice similarly infected. Twenty-eight of the 63 anemic mice survived and 14 of 63 control mice survived, as shown in figure 3. In a second experiment, the animals were made somewhat more anemic by shortening the interval between bleedings, and when these were infected 19 of 47 anemic mice survived and 2 of 48 control mice survived. In a third group of 47 anemic mice, three additional bleedings were performed after the animals were

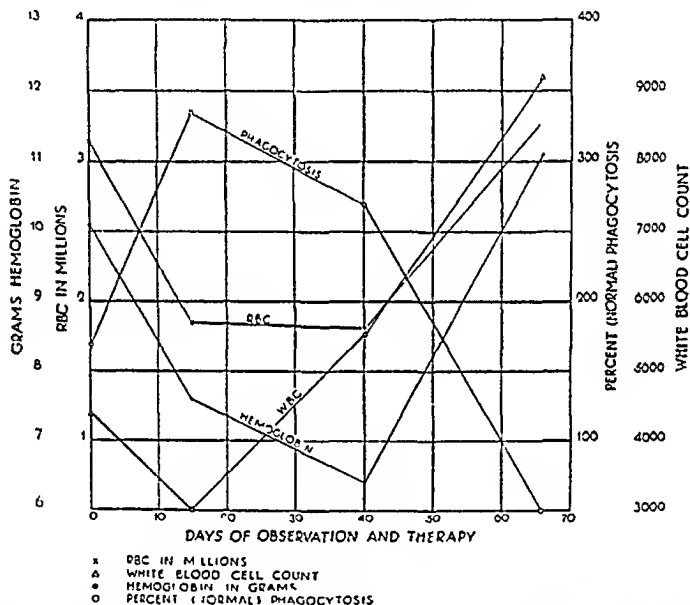


Fig 2*—Decrease in phagocytosis with therapeutically induced remission in a patient with macrocytic anemia

infected and only 5 of these survived. These results are summarized in figure 4. As the authors point out, these experiments do not prove that the increased phagocytic activity of the blood leucocytes observed in the anemic animals was responsible for the greater resistance to mouse typhoid but the parallelism was highly suggestive of some such relationship. Additional incomplete evidence for this interpretation was obtained by Sax and Berry (257) when no significant difference in antibody titer against an antigen of killed *Sal typhimurium* cells could be detected in normal and in anemic mice.

* From reference (18)

e Miscellaneous Factors

The action of cholesterol on phagocytosis was investigated by Horster and Dorbath (143) The blood of cats to which the cholesterol had been added in vitro or by intravenous injection had a lowered phagocytic activity when the concentration was 1% but with lower concentrations (10^{-4} to $10^{-6}\%$) the ac-

TABLE III†

(1) CASE	(2) DATE	(3) PHAGO- CYTIC ACT- IVITY	(4) "NOR- MAL" PHAGO- CYTIC ACTIVITY	(5) PER CENT "NOR- MAL"	(6) R B C (MIL- LIONS)	(7) HG (GM)	(8) W B C	(9) PER CENT (P M N)	(10) TYPE ANEMIA
1	5/3	22 38	9 93	225	1 74	7 8	5,300	51	Macrocytic hyperchromic
2	4/10	26 80	9 49	283	1 35	5 7	1,600	62	Macrocytic hyperchromic
3	6/27	21 81	8 50	257	2 43	7.8	3,850	55	Macrocytic hyperchromic
4	5/3	21 55	9 93	216	2 07	7 9	6,200	56	Macrocytic hyperchromic
5	6/25	15 70	8 80	178	2 54	11 6	3,500	62	Macrocytic hyperchromic
6	5/14	13 93	9 86	141	2 70	12 0	6,050	63	Macrocytic hyperchromic
7	6/27	11 88	8 50	140	2 63	10 1	7,400	62	Macrocytic hyperchromic
8	5/16	15 01	9 90	152	1 94	8 6	5,450	69	Macrocytic hyperchromic
9	4/30	9 94	8 14	122	4 47	8 0	7,900	72	Microcytic hypochromic
10	4/21	13 97	10 41	134	2 64	9 1	4,050	72	Macrocytic normochromic
11	5/2	20 51	11 08*	185	2 69	10 4	4,950	67	Macrocytic hyperchromic
12	5/2	20 17	11 08*	182	3 52	10 7	5,950	45	Macrocytic normochromic
13	5/17	17 81	7 14*	250	2 27	8 8	5,300	65	Macrocytic hyperchromic
14	5/17	24 24	7 14*	343	1 60	5.3	2,300	41	Macrocytic hyperchromic
15	5/23	17 39	10 10	172	3 69	8 3	6,900	49	Microcytic hypochromic
16	6/19	11 81	9 86	119	2 00	9 2	7,350	74	Macrocytic hyperchromic
17	6/15	13 06	8 91	148	2 52	6 9	6,500	85	Microcytic hypochromic, renal insufficiency,
18	4/25	13 27	8 99*	148	4 30	8 6	8,100	73	chronic G U infection
19	4/26	26 45	9 85	269	1 02	6 5	2,100	53	Microcytic hypochromic
20	5/14	17 54	9 86	178	3 15	10 7	3,000	64	Macrocytic hyperchromic
21	5/3	20 32	9 93	204	1 85	8 6	4,500	44	Macrocytic hyperchromic
22	5/14	22 78	9 86	231	3 19	8 6	—	34	Microcytic hypochromic
23	6/1	13 60	10 39	131	2 76	11 2	4,450	73	Macrocytic hyperchromic
24	4/17	16 35	11 67	153	1 11	4 6	6,150	75	Macrocytic hyperchromic
25	3/24	21 36	9 19	232	2 56	9 1	5,450	51	Macrocytic hyperchromic
26	4/26	19 38	9 85	197	0 79	3 3	3,250	49	Macrocytic hyperchromic
27	4/21	15 42	10 41	148	4 11	10 1	4,300	62	Macrocytic hyperchromic
28	5/23	14 73	10 10	146	4 20	6 5	6,500	30	Microcytic hypochromic
29	5/23	16 19	10 10	160	2 78	4 9	6,150	48	Microcytic hypochromic

† From reference (18)

* Control R B J All other controls L J B

tivity of the leucocytes was increased by 100% Lecithin was antagonistic to cholesterol so that the absolute concentration of the latter was of less importance than the ratio of the two compounds

In an extensive study of the effects of a gum acacia medium on the localization of Diplo pneumoniae type I in mice, Catron (41) found that the phago-

cytic cells and specific antibody response which were responsible for the localization and destruction of the bacteria in immunized mice inoculated with

TABLE IV*

The Effect of Normal and of Anemic Serum on Phagocytic Activity of Washed Neutrophils

TEST NUMBER	PHAGOCYtic ACTIVITY OF WASHED NORMAL LEUKOCYTES IN		PHAGOCYtic ACTIVITY OF WASHED ANEMIC LEUKOCYTES IN		PER CENT WHOLE BLOOD PHAGOCYTOSIS ANEMIC NORMAL
	Normal serum	Anemic serum	Normal serum	Anemic serum	
1	2	3	4	5	6
1	4 0 \pm 0 28	4 0 \pm 0 24	10 4 \pm 0 07	12 2 \pm 0 08	195
2	2 4 \pm 0 23	2 3 \pm 0 23	4 5 \pm 0 28	4 6 \pm 0 26	152
3	6 0 \pm 0 30	6 2 \pm 0 33	12 3 \pm 0 55	11 7 \pm 0 61	197
4	6 0 \pm 0 30	6 5 \pm 0 32	11 6 \pm 0 63	12 7 \pm 0 68	338
5	8 4 \pm 0 51	9 9 \pm 0 53	16 1 \pm 0 61	17 1 \pm 0 60	175
6	8 4 \pm 0 51	6 9 \pm 0 46	14 8 \pm 0 83	17 3 \pm 0 75	262
7	7 4 \pm 0 40	7 8 \pm 0 38	14 0 \pm 0 65	14 8 \pm 0 61	145
8	7 4 \pm 0 40	5 5 \pm 0 32	17 7 \pm 0 67	15 4 \pm 0 74	187
9	8 6 \pm 0 43	7 2 \pm 0 35	12 3 \pm 0 44	11 2 \pm 0 44	172
10a	7 6 \pm 0 61	13 6 \pm 0 66	12 4 \pm 0 51	11 7 \pm 0 41	173
10b	5 8 \pm 0 36	4 2 \pm 0 23	8 2 \pm 0 42	14 7 \pm 0 55	213

* From reference (20)

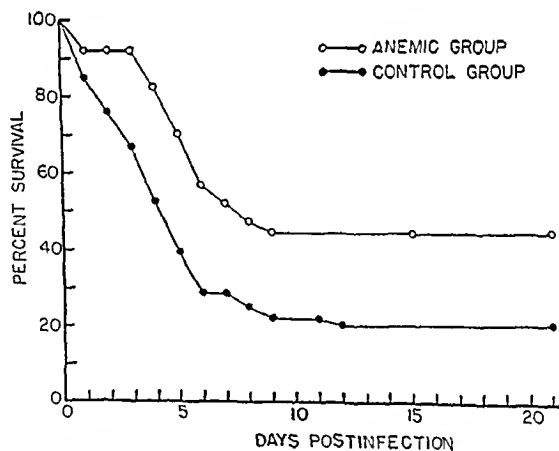


FIG 3*—The mice were infected intraperitoneally with a saline suspension of *Salmonella typhimurium*

a saline suspension of pneumococci were less effective against an inoculation of cells suspended in a viscous gum acacia medium. The explanation suggested

* From reference (22)

for these observations was the hindrance of diffusion by the viscous medium of immune bodies from the tissues into the inoculum which aided the phagocytes in overcoming the infection

A substance separated from the spleen was said by Medvedeva (197) to be capable of increasing the phagocytic activity of connective tissue and of raising the opsonic titer of blood when injected into experimental animals. Lymphatic tissue was endowed with the same properties but its action was always weaker. An emulsion of the whole non-fractionated spleen was most potent in promoting these changes but the splenic protein alone as well as the non-protein residue retained a reduced stimulatory effect on phagocytosis. The specificity of this

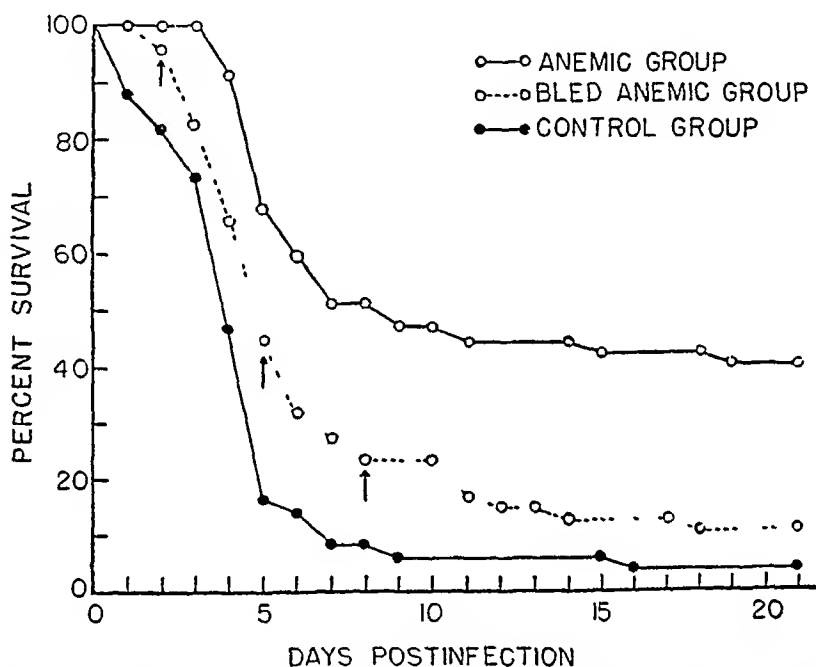


FIG 4 *—Same as figure 1. The arrows indicate the day that the mice in the bled anemic group had blood equal to 2 per cent of total body weight removed

action was not subjected to test by the introduction of other tissue macerates nor was the basis for the conclusions completely clear

8 The Phagocytic System as a Tool

a In testing antiseptics. In the preceding pages, the principal emphasis has been on work striving toward an elucidation of the mechanism of phagocytosis in situations or under conditions of importance to the intact organism in health or in disease. This is the category into which most experiments dealing with this subject naturally fall but there have been some investigators who have recognized in the phagocytic system a convenient means of achieving other ends. Nye (219) used it in conjunction with other tests in evaluating the *in vitro* activity of certain antiseptics in aqueous solution. Welch (296) subsequently recommended the use of whole blood mixed with artificially opsonized Staphylo-

* From reference (22)

Staphylococcus aureus for testing the toxic action of germicides. The concentration at which complete inhibition of phagocytosis occurred provided an index of the toxic effect. By comparing the indices obtained with guinea pig blood with those for human blood it was concluded that the germicide acted on the humoral rather than the cellular elements involved in phagocytosis. Human blood with its more resistant thermostable opsonin was not as susceptible to the action of the test compounds as was the more labile component of complement in guinea pig blood which accelerated phagocytosis. Welch, Brewer, and Hunter (301) reported that this technique enabled them to separate hemolytic complement from those components of plasma which brought about the more rapid phagocytosis (but see section 4c above). Welch and Hunter (299) (300) described improvements in the method of conducting these tests and presented data along with Welch and Brewer (302) (303) and Hirsch and Novak (140) on a number of different compounds. Sixty lots of penicillin sodium from ten manufacturers were examined by Welch, Davis and Price (304). Since the weight of the penicillin preparation which completely inhibited phagocytosis was essentially the same regardless of the type of potency, it was suggested that the inhibitory action resulted from an osmotic pressure effect. The concentrations required are not obtained in the ordinary clinical use of penicillin.

h. In diagnosis of brucellosis. Huddleson, Johnson and Hamann (146) compared the *in vitro* phagocytic action for *Brucella* organisms of citrated whole blood from patients known to have recovered from undulant fever in the past, from patients actively infected, and from those with no history of the disease. The absence of or a low phagocytic activity of the neutrophils obtained in conjunction with a negative allergic skin reaction was taken as evidence for susceptibility to *Brucella* infection. A positive skin test accompanied by low phagocytic activity indicated the presence of an infection and, as the latter increased, progress toward recovery was suggested. The following year Meyer, Stewart, Veazie and Eddie (203) recommended the same procedure in which the *Brucella suis* type culture of organisms was employed. When the average number of bacteria in 25-50 granulocytes was determined, the values were less than one for controls and varied from 1 to 28.4 in patients with clinical undulant fever or in recovered cases. Veazie and Meyer (287) substituted heparin for citrate as the anticoagulant for the test with the result that indices were more reproducible for infected animals and were higher with human blood. Variability, especially false negatives, was attributed to pH changes, partial clotting, too long delay, admixture of tissue juices, and length of incubation. An extensive survey for *Brucella* infection in 8124 individuals was carried out by Huddleson, Munger, Gould and Paulson (147). Of these, 845 (10.3%) were positive by the skin test and 7.1% were classified as infected on the basis of the phagocytic test, 2.7% were immune and 0.52% were questionably immune. Twenty-five neutrophils were examined in each of the smears and those containing 40 or more bacteria were designated as showing marked phagocytosis. In those subjects with a positive skin reaction, a diagnosis of infected was rendered when less than 40% of the polymorphonuclear leucocytes showed marked phagocyto-

sis, of questionably infected when 40-45% showed marked phagocytosis and if immune if 60% or more showed marked phagocytosis. As a means of speeding up the test and rendering the counts more accurate Cain (35) used a simple solution of toluidin blue in distilled water to stain thick, unfixed smears of the phagocytic mixture. The erythrocytes were hemolyzed, the leucocytes were lightly stained with none of the granules taking up the dye and the bacteria were dark blue. Pervushin (227) reported that the phagocytic test was valuable in the diagnosis of brucellosis while Jersild (154) believed that the use of heated patient serum, bacterial suspension and citrated blood without opsonin from some donor revealed the presence of an immune opsonin at a very early stage of the disease. He recommended these modifications of the original whole blood mixture. Munger and Huddleson (211) found that antigenic variants of *Brucella* were unsuitable for the phagocytic test since they were readily ingested by the leucocytes in normal human or guinea pig blood whereas the normal strains of *Brucella* were not.

c In testing the immune reaction in pertussis. Bradford and Slavin (32) observed that the opsono-cytophagic power of the blood increased during the course of pertussis and that it was generally greater in those who had had the disease than in those who had not. When immune blood was injected intravenously into a group of 9 infants, all were found by Bradford, Mikell, and Slavin (33) to have a higher phagocytic activity against *H. pertussis*. Intramuscular administration of adult immune blood or hyperimmune immune serum yielded less striking results but placental extracts produced a definite increase in the phagocytic power of the blood. Kendrick, Gibbs, and Sprick (160) and Singer-Brooks and Miller (267) independently reported the increase in opsono-cytophagic titer that accompanied vaccination with *H. pertussis* antigen. The titer was maintained about 6 months and declined considerably by the end of one or two years. Both publications mentioned the fact that in infants under 18 months of age the phagocytic power of the blood was very low or negative. In older children, more and more phagocytosis was observed until an age was reached at which it was impossible to differentiate those who had had the disease from those who had no record of an attack.

9 The Role of Phagocytosis in Disease

a Pneumonia It is not the purpose of the present report to discuss the pathology of pneumonia which of necessity would include as one aspect of the subject an analysis of the cellular defense mechanism. This alone would constitute an enormous undertaking which has already been done in the past and will no doubt be done again in the future by those better qualified for the task. There is justification, however, for reviewing some of the recent work carried out by Wood and his collaborators since a new type of phagocytosis seems to have been recognized and their results have appeared, for the most part, since the publication of Robertson's (248) paper on phagocytosis of foreign material in the lung.

In one of his earliest papers Wood (312) studied type I pneumococcus pneumonia experimentally.

with type specific antibody. Microscopic examination of the spreading lesion in control animals permitted identification of three characteristic zones (1) an outer "edema zone" containing many pneumococci floating freely in the edema fluid, (2) a middle zone made up of bacteria and actively phagocytizing leucocytes and (3) an inner zone of advanced consolidation with many leucocytes but no bacteria contained in the alveoli. No adequate explanation was found for the presence of active phagocytosis, presumably occurring in some cases without circulating antibodies, but obviously responsible for the clearing of the central part of the spreading lesion. A single dose of antipneumococcal serum given intravenously within 18 hours after inoculation protected the rats against the infection by agglutinating the bacteria particularly in the edema zone and permitting the leucocytes to destroy them by phagocytosis. The presence of specific opsonins greatly accelerated the phagocytic reaction which was accomplished primarily by polymorphonuclear cells since few macrophages had appeared by this time in the alveolar exudate. In a later publication, Wood and Irons (314) examined the effect of sulfonamide treatment instituted 6 hours after experimental infection on the pneumonic lesion in rats. At the end of 18 hours, the pneumococci in the edema zone gave evidence of bacteriostasis as shown by striking morphological changes and by the end of 42 hours of treatment, the edema zone had disappeared with the bacteria at the margin of the lesion having been overtaken by leucocytes. There was definite phagocytosis of pneumococci in the exudate around the periphery of the lesion. No pneumococci could be demonstrated by the fourth day and after one week only macrophages remained in the rapidly clearing alveoli. Pneumonic rats, previously rendered leucopenic by γ -irradiation, were used to demonstrate more clearly the phagocytic reaction in sulfonamide treated animals. The lesions were relatively acellular but the macrophages present had engulfed large numbers of the bacteria after 18-42 hours of treatment. The ingested pneumococci were ultimately destroyed with the result that the lesions were completely resolved. Since phagocytosis was observed in the lungs of animals with bacteremia, it was suggested that this occurred independent of circulating type-specific opsonins. Wood, McLeod and Irons (315) then demonstrated that such was the case and that the phagocytic mechanism functioned without either opsonization or injury to the pneumococcus capsule. This phenomenon was pursued further by Wood, Smith and Watson (316) with the conclusion that phagocytosis results from a direct action of the phagocyte upon the pneumococci. Phagocytosis in the absence of antibody was demonstrated not only in the lungs of living rats but also in formalin-fixed lungs, on the surfaces of a variety of tissues both freshly removed from the animals and previously "killed" with heat and on the surfaces of inert materials such as moistened filter paper, cloth and fiber glass. Smooth materials like cellophane, albumin, glass and paraffin failed to support the phagocytic reaction. From these observations, it was inferred that the physical character of the surface determined the activity of phagocytes in the absence of antibodies. The so called "surface phagocytosis" was found in additional studies to occur only on suitable surfaces while phagocytosis in the presence of

opsonins took place while the cells were floating free in a fluid medium. Direct visual observation of the process of surface phagocytosis revealed that ingestion proceeded only after the pneumococci were trapped by the leucocytes (or macrophages) against the alveolar wall. Subsequently, Wood and Smith (317) reported that bacteria trapped between the surfaces of phagocytic cells could also be ingested. Thus intercellular surface phagocytosis along with surface phagocytosis was believed to play a significant role in removing bacteria from the lung during chemotherapy of pneumonia. Similar studies on experimental Friedlander's bacillus pneumonia were carried out by Sale and Wood (254), Sale, Smith and Wood (255), and Smith and Wood (268). The phagocytic reaction in the absence of opsonization was again observed and was considered to be the primary factor responsible for the destruction of the microorganisms in the lung.

It is interesting to note that several years prior to the publication of the above work, Wright (319), in a lecture before a group of British physicians, stated that he no longer believed serum to be necessary for phagocytosis since in its absence he had observed what he termed "spontaneous phagocytosis." The experimental evidence for this contention was not given nor was any reference to it found. He also claimed that the phagocytes themselves were capable of altering their activity under various conditions. It seems to the writers that this is precisely the type of change induced in phagocytically active cells in anemia and possibly, in the reverse direction, in malnutrition.

If the phenomenon of "surface phagocytosis" is examined in the light of the theoretical formulation of Fenn (see section 1), one is forced to conclude that mechanical stimulation of the leucocyte surface results in a lowered surface energy which permits the entrance of the particle (pneumococcus) into the cell. This seems to occur only at the region of contact between phagocyte and surface, and not generally over the entire cell. "Smooth" surfaces incapable of eliciting this response would be unable to do so because of the absence of adequate mechanical disturbance. There is considerable experimental evidence in various branches of physiology that indicate changes of this type are not unlikely. By speculating further, one might anticipate that for a given set of conditions, variations of relatively small absolute magnitude in surface energy of the phagocytic cell would result in inherent differences in their phagocytic activity. Could this be the immediate basis for Wright's suggestion that cells are not phagocytically equal at all times and the reason leucocytes from anemic blood are more active? Until some means of evaluating these factors becomes available, the actual dynamics of the phagocytic process is doomed to remain in the realm of theory.

b Tuberculosis. In the following discussion only that part of the literature on tuberculosis which deals with phagocytosis will be considered. No special effort has been made to include all references to the subject.

Albert-Weil (4) noticed that phagocytosis of *Mycobact tuberculosis* by polymorphonuclear leucocytes was rapid and general while that by macrophages was slow and local. The former was considered to be essentially unfortunate

because the bacilli were especially toxic for them and the infection was spread by the migration of the neutrophils containing the microorganisms into the circulation. Therapy, therefore, should aim at combatting the polymorphonuclear reaction. Lurie (181) investigated the fate of living tubercle bacilli in the organs of reinfected rabbits and found that the immunity was a function of the increased capacity of the mononuclear phagocytes to destroy the bacteria and that it varied with the extent of the primary lesion. Polymorphonuclear leucocytes were of little importance in this process. Lowenstein (179) measured the uptake of starch granules by the phagocytic cells contained in the sputum of 42 tuberculous and 14 normal individuals after it had been shaken with saline and incubated at 37°C for 30 minutes with guinea pig serum as opsonin. The percent of phagocytosis was greater in those expectorating the large amounts of material and both micro- and macrophages were active. Caussimon (42) compared the phagocytic uptake of virulent *Mycobact tuberculosis* by polymorphonuclear and mononuclear leucocytes from healthy rabbits or guinea pigs with those from animals in an allergic period. There was moderate activity in the former case while in the latter the reaction was subject to wide variations ranging from intense to feeble to imperceptible but usually offering the best index of the reaction elicited by the allergic state. Serum from a tuberculous animal frequently endowed leucocytes from healthy animals with increased phagocytic ability. Too abundant phagocytosis by polymorphonuclear leucocytes in vivo caused diffusion of the tuberculous process. This confirmed the observation of Albert-Weil mentioned above. Hotopp and Kahn (144) determined the fate of phagocytized acid fast bacteria by the single cell method and found that *Mycobacterium marinum* remained viable inside the living polymorphonuclear leucocyte for a minimum of 20-45 hours, while the H-37 strain of human tubercle bacilli seemed to be definitely affected. *B. subtilis*, by way of comparison, would not grow after being engulfed by leucocytes. Clawson (47) focused his attention on the mononuclear cells and noted that the ingested tubercle bacilli undergo lysis at a greatly accelerated rate when immune serum is present at the time of phagocytosis. No difference was detected in the lytic power of monocytes from normal or immune and allergic animals. In contrast to these studies, Lurie (184) permitted mononuclear leucocytes obtained from sterile pleural exudates of normal and tuberculous rabbits to ingest tubercle bacilli and carbon particles in vitro in the presence of normal or immune serum. The fate of these bacilli was determined by inoculating the anterior chamber of the eye of a normal rabbit with these monocytes. Those from immune animals showed greater inhibitory ability than those from normals and cross serum reactions did not significantly alter the findings. When the tubercle bacilli and carbon particles were injected intravenously into normal and immune animals and with samples of bone marrow containing the phagocytized bacteria and particles collected 2 days later, comparable results were obtained after the marrow was introduced into the anterior chamber of the eye. Hughes (148) tested the ability of the serum of rabbits vaccinated by repeated injections of heat-killed tubercle bacilli to promote phagocytosis of the living bacteria by

polymorphonuclear and mononuclear blood cells. A progressive increase was found and the results indicated that the same antibody was concerned in the phagocytic behavior of the two types of cells. Woodruff (318) inoculated guinea pigs intraperitoneally with the H-37 strain of *Mycobact tuberculosis*. At first, the bacteria were subject to phagocytosis by neutrophils. This was followed by a period of growth during which no chemotactic influence was detected until the final period at the end when the bacilli again attracted the leucocytes. In guinea pigs rendered hypersensitive to tuberculosis, the period of free growth did not occur.

Active phagocytosis of tubercle bacilli by migrating cells and fibroblasts was observed by Kiraly (164) in tissue cultures of spleen and lungs of guinea pigs experimentally infected with bovine-type organisms. Epithelial cells, both fixed and detached, were also very active phagocytes. The phagocytosis was non-specific since carbon particles were engulfed equally as well.

Several studies have been carried out concerning the influence on phagocytosis of different types of antigens prepared with *Mycobact tuberculosis*. Shibata (266) obtained slight effect when rabbits were given a heated alcohol extract of a saponin culture or G bouillon culture of a high virulent strain. Dead bacilli were active while defatted bacilli, after prolonged hot alcohol treatment were not. Heat-killed BCG (*Bacille Calmette-Guérin*) strain, Shibata (264) found to increase markedly phagocytosis of either virulent or avirulent tubercle bacilli. The alcohol extract of this strain was also effective in promoting phagocytic activity which suggested that the waxy capsule, scarce in organisms from a saponin culture, possessed a remarkable antigenic action. It was finally shown (265) that living BCG bacteria were most active in inducing phagocytosis promoting substances in the blood of immunized animals. Torikata and Okumura (280) came to the opposite conclusion regarding the relative antigenic potency of living and killed BCG cells since they found that the latter were more easily phagocytosed than the former. The basis for these contentions seems to be more soundly established in the experiments of Shibata. Lurie (182) maintained that rabbits vaccinated with BCG are better able to immobilize bacilli of reinfection, inhibit their growth, and destroy them by the phagocytic activity of phagocytes which rapidly mobilize for the purpose. He also found (183) that mononuclear cells derived from actively tuberculous or vaccinated guinea pigs exhibited a greater in vitro phagocytic capacity for carbon particles than mononuclears from normal animals. This relationship also held for the ingestion of staphylococci and tubercle bacilli.

c *Streptococcus* infections. Much of the work done in association with sulfonamide therapy centered around infections with streptococci. That aspect of the subject has been covered in section 4a of this paper.

A minimal number of surviving leucocytes was necessary before Boys and Gunn (31) could demonstrate the bactericidal effect of defibrinated blood against *Strept hemolyticus*. The bacteria were phagocytosed and finally destroyed by intracellular lysis within white blood cells. Complement was not required for this action and even heating the serum at 68°C for 30 minutes did not impair the

bactericidal effect of the restored blood. Recent studies by Rothbard (251) (252) have greatly extended this earlier work. In the first place, heparin proved to be a more satisfactory anticoagulant than defibrination, potassium and ammonium oxalate, or sodium citrate in demonstrating the bacteriostasis of group A streptococci in the presence of convalescent serum. Blood from the rabbit, guinea pig or sheep could not be substituted for human blood in promoting bacteriostasis when human antibody was used. When human leucocytes were mixed with the plasma of each animal or when leucocytes from each of the animals were mixed with human plasma the final preparation was ineffective. In contrast to the findings of Boys and Gunn, complement and a thermostable factor found in human plasma were essential for inhibition of streptococcal growth in the presence of leucocytes and convalescent human serum. The thermostable component withstood storage at 4°C for 7 weeks but was destroyed by heating at 70°C for 30 minutes. It was also possible to prevent the bacteriostasis under these conditions by the addition of type specific M extracts or group-specific C carbohydrates of group A streptococci to the mixture. The inhibition depended merely upon the formation of a precipitate and it was not specific with respect to streptococcal type. In fact, stained films of blood cells treated with antigen-antibody preparations which formed a precipitate revealed neutrophils and monocytes loaded with large cytoplasmic vacuoles containing the precipitate. Such engorged cells were subsequently unable to phagocytose streptococci in homologous serum. Blood cells treated in the same manner, with the exception that no precipitate was formed, were phagocytically active against the microorganisms. Finally, leucocytes in the presence of both streptococci and antigen antibody precipitate were seen unselectively engulfing both types of particles until the capacity of the blood cell had been reached. It was thus apparent why the bacteria remaining outside the saturated phagocytic cells would be free to grow and reproduce.

Seastone (261) called attention to the fact that young streptococci were more resistant to phagocytosis than old ones and that the loss in resistance was coincident with the loss of or partial degeneration of the capsule. Homologous rabbit antiserum neutralized the anti-phagocytic property of the capsulated form in such a way that it appeared to be type specific. The absorption of the antiserum with an heterologous Strept. hemolyticus failed to remove the opsonizing property for the capsulated organism. That the capsule invariably inhibits phagocytosis was shown not to be true for all variants of hemolytic streptococci by Ward and Lyons (290). Four variants (designated as F, M, attenuated M, and C) were investigated and both F and M resisted phagocytosis in human blood. Attenuated M, which had a capsule as well developed as the virulent variants, was easily phagocytosed as was C which had no capsule. Lyons and Ward (186) next observed that an antiserum which protected mice against a virulent culture of the M variant of hemolytic streptococci contained a specific opsonin. Phagocytosis of the organisms was detected in the peritoneum of the protected mice. An antiserum prepared with the M variant as antigen opsonized both F and M variants of the strain.

While King, Green, and Henschel (162) detected no negative chemotropism to two strains of *Strept hemolyticus* using rabbit granulocytes, they did find a progressive toxic depression of phagocytosis which varied with the number of organisms present. McCutcheon, Coman and Dixon (189) reported that cells in a peritoneal exudate of rabbits exhibited a negative chemotaxis to some preparations of *Strept hemolyticus* but not to all. (For further reference to the chemotactic response of leucocytes to bacteria and bacterial products, see section 10b.)

The response of monkeys to primary respiratory tract infection with Group C hemolytic streptococci was characterized by Schwab, Saslaw, Woolpert, Merino and Doan (259), as consisting of a prompt but fleeting granulocytic leucocytosis with an occasional minor recurrent elevation in neutrophils. The phagocytic index was not significantly altered but the cellular reaction was thought to be primarily responsible for the successful defense against invasion. Saslaw and Doan (256) recently determined the role of phagocytosis in resistance to reinfection of monkeys with the same microorganism. They found that a greater bacterial phagocytosis occurred under such conditions but that the response was not as great as would be expected from evaluation of the opsonic index alone. In contrast to the conclusions drawn by Wood in his studies of pneumonia (see section 9a) these authors believed the highly specific humoral antibodies greatly facilitated the phenomenon of spontaneous cellular phagocytosis with the result that fewer polymorphonuclear leucocytes were needed to combat the second infection than the first. They further believed that the younger mature neutrophils were definitely more phagocytic and would undergo a progressive decline as the individual age increased. (See section 7c for comparison.)

d Protozoan infections (1) Malaria. de Langen (60) states that, in the preparations he examined, neutrophilic leucocytes definitely participated in the phagocytosis of malarial parasites. Whether this occurs only in exceptional cases when the blood is flooded with merozoites or also takes place when there is not such massive infection, he was unable to determine. He did suggest, however, that it was probably an uncommon phenomenon. See-Lu (262) believed that phagocytosis of malarial parasites occurred only in extremely severe cases and shortly before death. It was seen in 4 cases, three of which were brought to his hospital in a coma, and died without regaining consciousness, and the material from the fourth was sent to him from another Chinese province without the patient having been seen. Neutrophils were principally active, the monocytes next and the lymphocytes were limited. Dividing parasites were frequently seen in granulocytes but they were mostly digested in the monocytes with only pigment aggregates remaining. No sexual forms were found but the schizonts were extraordinarily numerous, about one-fifth of the erythrocytes being infected. Osgood (223) observed the presence of malarial parasites, in all stages of digestion, in neutrophils from the sternal marrow of each of five cases of inoculation tertian malaria studied. Most of the phagocytes were staff cells but segmented forms and metamyelocytes were also active. Peripheral

blood smear examinations made at the same time gave no evidence of phagocytosis except for the occasional presence of pigment granules

The suppression of *Plasmodium basiliannum* infection in various species of Panamanian monkeys was attributed to phagocytosis of the parasites, both extracorporeal (merozoites free in the plasma) and all stages of intracorporeal, according to Taliaferro and Cannon (276). This was accomplished by macrophages, primarily of the spleen, to a less extent of the liver and to a still lesser extent of the bone marrow. During the acute rise of the infection, the parasites were concentrated in the spleen, with some in the liver and bone marrow, where they were sluggishly phagocytosed. At the crisis, the plasmodia were regionally concentrated in the spleen and held in the Billroth cords but did not pass into the venous sinuses. They were either agglutinated or adhered to the macrophages which aggressively ingested them after a day or two or sometimes more. The macrophages of the liver and bone marrow were also more phagocytic at this time. All stages of parasites in all stages of digestion engorged the macrophages and the infection was usually rapidly overcome, once crisis phagocytosis was initiated. After superinfection, active concentration and phagocytosis began within an hour instead of waiting for several days which indicated that acquired immunity took time to develop but responded immediately, once it was established. This immunity depended upon an increased rate of phagocytosis by the individual macrophages in the spleen, liver and bone marrow and an increased number of macrophages in the spleen and bone marrow. These findings were confirmed by Tupa and Ciuca (285) in their studies of experimental infections of *M. rhesus* with *Plasmodium Knowlesi*. Herrera (136) pointed out that active phagocytosis of parasites is one of the chief accompaniments of immunity in malaria and said that this could be especially observed in the large mononuclears in malarial blood. As he suggested, phagocytic observations may serve as a guide to establish the degree of immunity, the type of parasite and the approximate size of dose of the medicament.

(2) Trypanosome infections. Hasskó (133) found that trypanosome infections in mice influenced neither the phagocytic ability of the mesenchyme system nor the distribution of chemo-therapeutic agents. This was in direct contrast to the results he obtained in spirochaetal diseases (see below). Jancsó and Jancsó (151) reported that in mice, treated for *Trypanosoma brucei* infection with germanin, the phagocytes of the reticulo endothelial system played an important role in the curative mechanism. The drug was believed to have an opsonin-like action on the parasites which rendered them more easily ingested alive by the cells in the spleen and liver. Treatment with electro-colloidal copper, a recognized poison for the reticulo endothelial system (see section 4c (2)), practically eliminated the natural mechanisms of defense with the result that both phagocytosis of trypanosomes and the production of immune bodies were abolished. The same general effect was obtained by splenectomy. Culbertson (54) attributed the gradual increase in resistance with age in rats to *T. lewisi* infections to the enhancement in the phagocytic capacity of the host's cells. This conclusion was based on the fact that the Kupffer cells of nursing

animals were less able to ingest particles of trypan blue than the Kupffer cells of older animals

Neitz (214) observed that large mononuclear and neutrophilic leucocytes phagocytosed *Piroplasma canis* in a case of malignant jaundice in a dog. The former cells ingested the intracellular parasites while the latter were active against the extracellular forms. Liew (175) demonstrated that phagocytosis of Leishman-Donovan bodies by altered microglia cells occurred upon intracerebral injection of non-flagellated forms into Chinese hamsters.

(3) *Spirochaete* infections. Manouelian (194), in a study of hereditary syphilis, noticed active phagocytosis of *T. pallidum* in the placenta while the tissues and organs of the fetus were intensively septicemic and showed no signs of defense activity. He suggested that a substance in placental veins sensitized the treponemas and rendered them more easily ingested. Cunningham, Morgan, Tompkins and Harris (55) observed large numbers of phagocytic mononuclear cells (clasmatocytes and macrophages) in the lesions of experimental syphilis in the rabbit. These cells were more numerous than in normal tissue and were greatly stimulated in their phagocytic capacity.

Relapsing fever hindered the phagocytic ability of the Kupffer cells of the liver and of the peri-follicular cells of the spleen, according to Hasskó (133), and also altered the deposition of drugs regularly deposited in reticulo-endothelial cells. This constituted a transitory change, however, for the phagocytic action returned to normal a short time after the infection. Kritschewski and Awrech (169) could detect no phagocytosis of spirochaetes injected into animals immune to relapsing fever. This led to additional *in vitro* and *in vivo* experiments in which exudative leucocytes were assessed against *Spirochaeta duttoni*. Results showed the phagocytic activity of cells from immune animals, recovered from relapsing fever, to be the same as that of normal animals. Himmelweit (139), on the other hand, found that macrophages grown in tissue culture from the spleen of normal, immune, and spirochaete infected chickens were more active in taking up the parasites when derived from immune animals. He also observed immediate phagocytosis of spirochaetes by macrophages of normal tissue when immune serum was added. This suggested that opsonization by anti-spirochaete antibodies was responsible.

e Helminthic infection. Africa and de Leon (3) studied the mechanism of phagocytosis of various helminth ova under both experimental and natural conditions. The process by means of which the foreign-body-giant-cells ingested the eggs varied with the size, structure and chemical composition of the ova. The phagocytes attacking the eggs of *Ascaris* and *Fasciola* appeared healthier, better nourished and more powerful than those attacking *Schistosoma* eggs. These differences were attributed to the variance in potency of toxic substances excreted from the ova. It was also suggested that the giant cells engulfed the foreign bodies and digested them for nourishment.

f Virus infections. Fairbrother (84) reported experiments which indicated that phagocytosis is an important defense against vaccinia virus. Serum was more obviously viricidal when leucocytes were present than when they were

absent which implied that the serum sensitized the vaccinia to cellular destruction. Sabin (253), however, came to the opposite conclusion. His experiments showed the leucocytes to be capable of "fixing" the virus but not of destroying it since they remained highly infectious for as long as 24 hours. There was no evidence for the belief that the immune serum of an animal exerted an opsonic action on vaccinia or that the leucocytes could destroy the virus in its presence. In a somewhat different approach to the problem, Wilson, Saslaw, Doan, Woolpert and Schwab (308) found that infections with influenza virus definitely lowered both the cellular and humoral defense elements in monkeys to reinfection with *Streptococcus hemolyticus*, group C. Doan, Saslaw, Beard, Woolpert, Schwab and Merino (71) had previously reported a decrease in the opsonocytophagic index under similar experimental conditions.

10 Phagocytosis and Immunity

In some of the preceding sections of this paper, reference has been made to the importance of opsonins in increasing phagocytosis. The mechanism of this action was considered at length in the review of Mudd, McCutcheon and Lucké (210). Cannon (39), as previously mentioned, has more recently emphasized the functional aspects of the humoral defense mechanism which included certain phagocytic relationships. Additional phases of this problem, not previously treated, will be taken up below.

a. The importance of strains in determining bacterial susceptibility to phagocytosis. There are undoubtedly many factors governing the virulence of different strains of the same species of pathogenic bacteria, as any of the modern textbooks of bacteriology will attest. The ease with which a strain may be ingested by phagocytic cells seems to be one of these factors even though all the experimental evidence is not in agreement on this point. For example, Spink (269) found no appreciable difference in the phagocytosis of pathogenic strains of staphylococci as compared to non-pathogenic strains. He used the leucocytes of defibrinated human blood and tested not only strains possessing potent hemolytic and lethal exotoxins but young and old cultures as well. There may have been a lower percentage of active granulocytes when pathogens were used but the mean number of bacteria per cell was the same with all strains. Weinbrenner (293) came to the opposite conclusion when he observed more phagocytosis of saprophytic *Staph. albus* strains than with virulent *Staph. aureus* strains. However, the differences in phagocytosis of smooth and rough variants of *Salmonella enteritidis* could not be correlated with differences in virulence, surface tension or spontaneous agglutination. In spite of the fact that physico-chemical factors such as electrolyte balance, pH, osmotic pressure, and specific opsonins were shown to influence phagocytosis, Weinbrenner maintained that biological factors were of primary importance. Hale and Smith (124) investigated the influence of coagulase on the ingestion of staphylococci and found that positive strains in the presence of coagulable plasma were less easily phagocytosed than negative strains. The initial protection afforded the bacteria was specific and did not depend upon a physical alteration of the medium since other species of microorganisms present at the same time were readily

engulfed The inhibitory action was demonstrable with the plasmas of certain species not normally coagulable provided a little coagulase activator was added to the phagocytic mixture

Peritoneal exudates from guinea pigs, rich in polymorphonuclear leucocytes, were suspended in Locke's solution by Delaunay (65) to compare the phagocytosis of smooth and rough forms of *Salmonella paratyphi* B and *Shigella dysenteriae* Only the rough forms were taken in and digested while the other types were refused Living staphylococci were ingested at the same time the leucocytes avoided the smooth strains The author attributed the inhibition of phagocytosis to a glucide-lipid antigen which coated the bacteria Maltaner (193) had similar results with smooth and rough strains of *Eberthella typhi* since only the latter were vigorously phagocytosed when injected into the peritoneal cavity of normal guinea pigs However, there was no difference in phagocytosis of the two strains inoculated into immune animals Pike and Mackenzie (233), on the other hand, were unable to detect any variation in resistance to phagocytosis between a smooth strain of *Salmonella typhimurium* of high virulence and a smooth strain of low virulence. In this case, virulence was attributed to an unmistakable ability to multiply in the host. Delaunay (66) found that a strain of *E typhi* which contained only the O (somatic) and H (flagellar) antigens was not phagocytosed until an antiserum containing the O antibody or both O and H antibodies was added to the mixture An antiserum containing only the H antibody (the O antibody having been absorbed by the addition of O antigen) had no more opsonizing action than normal non-immune serum This demonstration merely confirmed the earlier work of Bhatnager (24) and Dennis and Senekjian (69), who had previously shown that the O antibody and not the H antibody enhanced the phagocytosis of *E typhi* The former writer also stated that phagocytosis was intimately associated with agglutinability by O antibody since inagglutinable strains were also highly resistant to ingestion by leucocytes While studying the "VI" antigen of *E typhi*, Felix and Bhatnager (85) found a powerful phagocytosis-promoting action of V₁ antibody exerted on strains containing the antigen but it was without effect on strains devoid of the antigen The V₁ antibody proved to be more potent in promoting phagocytosis than the O antibody, however, there was a summation of their action which seemed to be essentially similar, since both depended upon the active participation of complement Formolized V₁ antigen was less efficient than the V₁ antigen contained in living virulent bacteria in giving rise to antibody capable of increasing phagocytosis, while the agglutinating properties of the two antibodies were identical According to Sugie (273), the addition of complement was capable of restoring the opsonizing action of typhoid immune serum partially inactivated by heat (56°C for 30 minutes) but this was not observed in heated normal serum A basic difference in the two types of phagocytosis was suggested In addition, the antigenic structure of the strain of *E typhi* used in immunization was reported to be important in determining the opsonizing potency of the serum

In studies of the pathogenicity of various strains of *Corynebacterium diph-*

theriae in guinea pigs, Ørskov, Anderson, and Poulsen (222) observed that the gravis strain was much more resistant to phagocytosis than the intermedius and mitis types. Orr-Ewing (220) came to the same conclusion after studies were made with blood from a number of different persons.

b. Anti-phagocytic substances. Why certain strains of some pathogens may be more resistant to phagocytosis than others may be explained by the toxic action exerted by the bacteria or by bacterial products on the leucocytes. Filtrates of staphylococci cultures exert a depressing effect on phagocytosis *in vitro*, according to Pike (232), who also showed that the depressing agent was not antigenic, did not deteriorate on standing and was thermostable. A similar substance was produced by *E. coli*. Panton and Valentine (225) compared the human lesions produced by staphylococci and found that strains yielding strong leucocidins and weak hemolysins were commonly associated with severe acute infections and the reverse combination with longstanding superficial infections of the syctic type. Delaunay (61) explained the greater resistance of immunized rabbits than of normal controls against intracutaneous injections of 0.1 cc. of a suspension of toxin producing staphylococci as due to the action of anti-toxin which permits the phagocytic power of accumulated leucocytes, otherwise inhibited, to overcome the bacteria at the site of the inoculation. The same explanation was given by Stewart (271) in her studies on the mechanism of antitoxic immunity in *Cl. welchii* infections in guinea pigs and also by Kropp and Smith (170) in similar experiments. Hammerschmidt (125) believed that the defense against diphtheria depended upon the phagocytic activity of the leucocytes and that in normal animals the white blood cells were paralyzed by the toxin. Immunization led to neutralization of the toxin which resulted in normal phagocytosis without the intervention of phagocytosis promoting antibodies. The experimental evidence for this is not at all clear.

The necessity for the production within the animal body of two kinds of antibodies before phagocytosis of virulent bacteria,—like pneumococci, staphylococci and *B. anthracis*—is possible was pointed out by Pettersson (228). One of these must first neutralize a "negatactic" substance, produced by the pathogen, before the leucocyte can close in on the microorganisms and the other antibody must neutralize an antiphagocytic product of the bacteria before ingestion can take place. Additional experiments (229) indicated the loss of antigenic action of the negatactic substance produced by anthrax bacilli from heating at 68°C for 30 minutes. An albumin precipitate obtained by acetone treatment of anthrax pus contained a negatactic substance capable of inducing immunity in animals immunized with solutions of the material. Subsequently, Pettersson (231) identified the phagocytosis inhibiting substance from pneumococci as the same as Heidelberger's polysaccharide. In the same publication, he qualified his original generalizations concerning the existence of a negatactic reaction in all animals as being confined to rabbits and man while in guinea pigs and mice, for example, the leucocytes could come into contact with the bacteria (in this case pneumococci) but could not engulf them because of the action of the polysaccharide. Immunity in these animals would therefore involve only

one antibody as far as phagocytosis is concerned. Therapeutic serum for man, however, should have both antibodies present so as to render the cellular defense mechanism active (230). In the same year, Stevenson and Reed (270) suggested that strains of staphylococci possessing high virulence, elaborated a potent hemolytic toxin which also exerted a negative chemotactic action rather than the dual substances postulated by Pettersson. The toxins from different bacteria were found by Delaunay (64) to elicit all possible types of chemotactic response in leucocytes. That of *Corynebacterium ovis* caused an accumulation of polymorphonuclear leucocytes when injected intradermally in guinea pigs, diphtheria toxin in non-immunized guinea pigs prevented an afflux of white blood cells to the region of injection, and tetanus toxin injected intradermally had neither chemotactic nor necrotic action. Toxin proteins of bacterial origin were also found capable, by Delaunay (64), of inhibiting leucocyte chemotaxis. Subsequently, Delaunay, Sarciron, and Pages (67) observed that sublethal doses of any glucide-lipid antigen, injected into mice or guinea pigs, rendered the animals susceptible to fatal injections with a dose of pathogenic bacteria not ordinarily dangerous. The antigen was said to inhibit diapedesis of the granulocytes but not to reduce the phagocytic ability of the reticulo-endothelial cells for intravenously injected bacteria, dyes or other foreign particles. Delaunay (62) had previously reported that an antigen of this type failed to alter the ingestion of living staphylococci or anthrax bacilli by leucocytes in a peritoneal exudate acting either *in vivo* or *in vitro*. A summarizing statement by Boivin and Delaunay (29) of the importance of inhibition of diapedesis in the pathogenic mechanism of bacteria has recently appeared.

c. The fate of ingested particles. Reference has already been made to differences in the speed with which phagocytes kill ingested microorganisms (see sections 9b and 12a (1)), however, it should be apparent that generalizations are not only misleading but impossible. A number of variables complicate this problem, which, after all, is the final act of the cellular defense mechanism. The engulfment of a pathogenic bacterium by a leucocyte is merely the step that must be accomplished before the bacterium can be destroyed. One might expect tubercle bacilli to be more resistant to digestion within the phagocytic cell, because of its waxy content, than some species of bacteria less well protected. The various cell types that are concerned with phagocytosis might also differ in their digestive capacity. When the question of the influence of immunity on the ultimate destruction of the microbe is considered, another complication is added which must also be taken into account. It is not particularly surprising, therefore, that relatively few investigations have been focussed on the quantitative aspects of this problem since abundant qualitative evidence is available which proves that destruction ultimately occurs. If this is protracted as Fothergill, Chandler and Dingle (92) believed in the case of *H. influenzae*, the bacteria might merely be protected from the destructive action of the antiserum by their refuge within the phagocytes. This was suggested as the basis of failure frequently observed in meningitis due to this organism.

The single investigation that was found on the importance of immunity in the

digestion of bacteria engulfed by phagocytes is the work of Rohetson and van Sant (249). The action of macrophages and polymorphonuclear leucocytes from normal and immune dogs was compared. The cellular exudates were produced by intrapleural injections of either gum arabic or aleuronat. Observations were carried out employing a highly virulent *Diplo pneumoniae* type I. Macrophages had a much more pronounced ability to digest the bacteria than the polymorphonuclears and this difference was most marked in the presence of opsonic fluids of relatively low concentrations. Higher titers resulted in a more uniform behavior.

Exudates, induced in rabbits, were used by Weiss (294) for determining the proteinase and peptidase activity of polymorphonuclear leucocytes, monocytes and epithelioid cells. A cathepsin was contained in each cell type and a common dipeptidase which hydrolyzed L-alanyl-glycine. Monocytes were differentiated from neutrophils by the pH at which the dipeptide was split. Epithelioid cells were comparable in enzyme pattern to the former. Hicks and Opie (138) demonstrated an increased proteolysis *in vitro* by splenic tissue which paralleled the increased phagocytosis of red and white blood corpuscles in the spleen after intravenous injection of these cells in rabbits. The increased proteolysis was caused by a proteolytic enzyme present in the macrophages of the organ and it was maintained at a high level 6-24 hours following the injection but returned to normal after 48 hours. No phospholipid splitting enzyme could be detected by Hicks (137) in the macrophages which accumulated around punctured wound tracks in the brains of mice.

11 Studies on the Phagocytic Behavior of the Cells of the Reticulo endothelial System

Reference has already been made in several preceding sections to the important role played by the reticulo endothelial system in combatting infectious diseases. Only a few selected publications dealing primarily with the phagocytic functions of the cells apart from infections will be included in the presentation which follows. For one of the most comprehensive treatments of this system, the reader is referred to Jaffé (150). The inflammatory reaction has been reviewed by Menkin (200) (201).

a. *Macrophages* In an interesting study on the involution of the uterus in the mouse, Deno (70) described three major agencies which participated in the process. (1) neutrophils digested and eliminated the cellular debris during the first 2 days of the puerperium, (2) the exfoliation of polypoid masses of thrombosed vessels and other necrotic residuum through undermining by the endometrium during the first few days post-partum, and (3) the phagocytosis and digestion by macrophages of erythrocytes and other cells or cell fragments after the second day following parturition. The injured and disorganized placental site was transformed into the mesometrial reticulo-endothelial nodule characteristic of the puerperium after a few days. The macrophages, filled with hemosiderin formed as a result of erythrocyte digestion, remained in masses at the base of the mesentery for several months or possibly for the life-time of the animal. These made up the small brown hemosiderotic areas that were visible

on the dorsal surface of the uterus The exact origin of these cells was undetermined

Vassos (286) observed phagocytosis by macrophages of collagen as well as many of the break-down products formed in the base of large peptic ulcers, the bed of which undoubtedly had been previously attacked and partly digested by gastric enzymes He was unable to ascertain whether the process was destructive or reparative

Macrophages in the lymph nodes in the appendix of rabbits were found by Baker and Enticknap (13) to engulf species of bacteria which gave the same staining reaction as most of the microbial population in the rabbit's caecum Granulocytes contained bacteria

It has long been known that the spleen is responsible for the removal of old erythrocytes, and possibly leucocytes, from the circulation This phenomenon was investigated experimentally by Wehrle (292) Injections of rabbit corpuscles into the blood stream of rabbits resulted in a greatly increased rate of phagocytosis which reached a maximum 16-18 hours after the injection It was most pronounced in the splenic cords but occurred to a smaller degree in the sinuses It has also been recognized for some time that a hyperactive spleen may destroy excessive numbers of erythrocytes thus leading to an anemia Sennott (263) recently added three cases of hemolytic anemia in the newborn to those already reported and found definite evidence of erythrophagocytosis in each

The transformation of histiocytes, which accumulated in the omentum of rats following injections of particulate matter, into macrophages was observed by Baillif (12) These phagocytes collected just beneath the surface and engulfed the material entering through and between the mesothelial cells Secondary collections appeared about the smaller blood vessels and took up the particles which had traversed the vascular walls The *taches laiteuses* increased in size and produced numerous macrophages Marshall (195) recently made use of silver carbonate and ammoniacal silver techniques to demonstrate two types of argyrophile cells in the lungs of man, the rabbit and the cat These cells closely resembled cells of the reticulo-endothelial system elsewhere in the body, including microglia (see below), which may be demonstrated in the same way These cells stored vital dyes and formed alveolar phagocytes

A recent study by Houghton (145) on the functional and morphologic behavior of macrophages in response to antigen has been reported A peritoneal exudate of rabbits containing a heavy suspension of cells (78% clasmatocytes) was cultivated in Carrel micro-flasks containing a medium of 60% non-immune rabbit serum in Tyrode solution Serum residues from the cultures yielded immune bodies on the sixth day and precipitins were subsequently observed, paralleling their appearance in the serum of immunized animals Macrophages were considered responsible for this phenomenon

b Microglia A number of references and an extensive discussion on the nature and origin of microglia may be found in the paper by Dougherty (78) These cells have been classified as part of the reticulo-endothelial system be-

cause they are capable of ingesting particulate matter and because their origin is similar to that of other cells belonging to this system. Belezky (16), for example, reported that phagocytosis of spirochaetes affected by microglia cells was prevalent in the central nervous system of paralytic patients coming to autopsy in an institution for the insane.

Mogilnitskiĭ, Zhdanov, and Markuze (208) found, on histological examination of the brains of rats previously sensitized to foreign proteins, and subjected to experimental cerebral lesions, more rapid absorption of injured brain substance than in rats similarly injured but not sensitized. This was attributed to the greater activity of the brain phagocytes in the experimental animals as compared to the controls. The phagocytes were identified as part of the reticulo-endothelial system. Lebowich (172) similarly demonstrated phagocytosis by microglia cells in experimental lesions of the rabbit brain. Dye particles, blood pigment granules, and bacteria were ingested by some transitional forms of microglia but not by neuroglia and oligodendroglia cells (for comparison, see the work of Andrew quoted below).

Dunning and Furth (80) used silver carbonate staining on fixed tissues and concluded that the histiocytes in the liver and peritoneal membrane of a chick embryo and in the peritoneal membrane of a rabbit are morphologically identical with microglia in the brains of chick and guinea pig embryos. The behavior of these cells in tissue cultures of several organs served as confirmation.

Andrew (7) described neuronophagia by microglia in the cerebral cortex of starved mice. It was interpreted as essentially a process of cytolysis of nerve cells with the nucleus being the most resistant structure to the process of phagocytosis. Normal, or almost normal, nerve cells, as far as structure is concerned, were seen being phagocytosed by a single microglia or jointly by 5 or 6 of them. Purkinje cells were not ingested. The same phenomenon was observed in the brains of normal senile mice but it is a much slower process than in starving animals. Andrew and Cardwell (9) were able to demonstrate neuronophagia in the human cerebral cortex in senility and in a number of pathological conditions. It was most active in the layer of polymorphic cells. Andrew (8) later reported that the oligodendroglia carried on a definite phagocytic activity in the cerebrum, medulla oblongata, and spinal cord in the mouse during both rapid and prolonged starvation. Amphyocytes were the phagocytic cells in the semilunar ganglion.

In cultures of spinal ganglia and peripheral nerve cells of 12-15 day chick embryos, Weiss (295) found large numbers of macrophages produced within 2-3 days. The cultures were carried on the surface of cover glasses in a liquid medium consisting of 1 part of blood serum and 5 parts of Tyrode solution. Many of the macrophages were seen to originate by transformation from spindle cells of the fibroblast or sheath cell type. Ingestion of carmine granules by the transformed parts was observed. Contact between the spindle cell and a smooth surface was said to elicit the formation of the macrophage.

12 Phagocytic Functions in Lower Animals

a. Lower vertebrates (1) Chick embryos. For more than a decade the

chick embryo and its membranes has been employed as one of the most suitable and convenient means of culturing a variety of bacteria, viruses, tumors, etc., otherwise difficult or impossible to maintain. The name of Goodpasture is intimately linked with the development and elaboration of this technique. One of his important contributions, particularly from the standpoint of the present review, was published in collaboration with Anderson (108) in which the chorio-allantoic membrane of chick embryos was inoculated with pure cultures of pathogenic bacteria as a means of studying problems of infections, especially the early stages of invasion. In certain instances phagocytosis favored rather than resisted infection because the bacteria found favorable and possibly necessary media for invading the living host within either mesodermal or epithelial cells, or both. Organisms of this type included *Strept viridans*, *E typhi*, *Br abortus*, and *Myco tuberculosis avium*. Neither *Staph aureus* nor *Strept hemolyticus* appeared capable of growing in an intracellular medium in this host and were destroyed, at least in part, by the phagocytes.

In an earlier study by Heine (135) chick embryos of various ages were injected with India ink, incubated for a short time and then fixed for histological study. Ink particles were observed in cells in all three germ layers immediately after the germ layers were formed. This indicated that the acquisition of phagocytic ability was not a gradual process during development. Even in the unincubated blastoderm, cells of both ectoderm and entoderm took up ink particles. In later embryonic stages, the capacity for phagocytosis was gradually restricted to mesenchyme and endothelial cells and to leucocytes. In young embryos, the India ink stimulated within the cells of the ectoderm, amnion and chorion an atypical and accelerated proliferation. Such cells were also capable of phagocytic activity. More recently, Canat and Opie (37) described the inflammatory reaction induced in chick embryos by particulate matter and by chemical agents. Cells having the characteristics of histiocytes ingested foreign particles and even engulfed and digested erythrocytes and other cells in embryos 3 days old. Granulocytes took little, if any, part in this reaction and were first seen in small numbers at the site of inflammation in embryos 6-8 days old. Within a few days of hatching, granulocytes assumed the important role characteristic of postembryonic inflammation. The same authors (38) followed the fate of avian tubercle bacilli introduced into chick embryos of different ages. The large histiocyte-like cells in young embryos, mentioned above, contained great numbers of the bacilli which, in agreement with Goodpasture and Anderson (loc cit), were thought to be multiplying intracellularly. An increase in resistance to multiplication and invasion by avian tubercle bacilli parallel the increase in number of granulocytes.

(2) Amphibians. Comolli and Santoro (50) reported the results of studies on the leucocytes of the toad, *Bufo arenarum*. Supravital stains differentiated the various types of white blood cells and amoeboid movements were seen in all except the basophiles. Phagocytosis of India ink and bacteria was not particularly active *in vitro* but the former was more rapidly ingested *in vivo*.

Kaether (156) used intravenous India ink injections to determine the strength

of the phagocytic reaction of the reticulo endothelial system of the frog, *Rana temporaria*, when various human sera were part of the suspending fluid. Only a moderate reaction was observed with the serum of healthy persons while a more potent reaction accompanied the use of serum from cases with latent and febrile infections. In the latter conditions, a humoral activator was postulated as responsible for the greater phagocytic activity.

(3) Fish. Phiszka (235) immunized carp against *Pseudomonas punctata* infections and, after determining the conditions for obtaining optimum agglutinin titers, noticed that phagocytic activity also was improved.

(4) Cyclostome. Various substances, such as ammoniacal citrate of iron, trypan blue, and bacteria, were injected into the body cavity of ammocoete larvae of *Lampetra planeri* (Bloek) (one of the lampreys) by Gérard (100) in order to study the distribution and function of what he termed the athrophagocytic system. This was defined as the power of collecting and storing moderately or highly dispersed substances. Endothelial cells of the cavernous tissues of the branchial arteries and the reticular coils of the hematopoietic tissue of the spiral valve, of the mesonephros, and of the pronephros were found to have athrophagocytic power.

b Invertebrates. Starting with Metchnikoff's theory that the few animals capable of digesting what should be immune to tuberculosis and with Metchnikoff's discovery that tubercle bacilli, injected into the body cavity of the wax-eating *Galleria mellonella*, were rapidly destroyed by the leucocytes, Biron (26) studied the various reactions produced in the same species of caterpillars by six types of *Mycobacterium tuberculosis*: Vallee, human, avian, piscine, BCG and "homogene". Injections of Vallee, human or BCG organisms were followed by active phagocytosis and formation of giant cells and capsules within which the bacilli lost their acid-fast property. Piscine bacilli produced the same reaction and also a marked vacuolization of the phagocytes while the avian strain produced a marked vacuolization of the leucocytes but were rarely or never phagocytized. They were rapidly lysed by the plasma. The "homogeneous" bacilli were more virulent than any of the other types tested. They multiplied in the caterpillar's blood and retained their acid-fastness for long periods. Cameron (36) investigated the phagocytic ability of different cells in the caterpillars of *Lepidoptera* and found the following to be effective: (1) lymphocytes, leucocytes (Cameron's designation), and spherule cells in the blood, (2) pericardial cells, and (3) certain cells of the fat body. Blood cells were most active, taking foreign particles, cells and bacteria soon after they were introduced into the body cavity. While the spherule cells were not actively phagocytic as a rule, both lymphocytes and leucocytes were and the proportion of lymphocytes increased rapidly during the period of ingestion but returned to normal once the foreign material had been removed from the blood. The pericardial cells were phagocytic for some bacteria, especially acid-fast organisms which survived intracellularly throughout metamorphosis of the larvae and could be isolated from the imago in the living, virulent state. A wide range of behavior was observed with different bacterial infections. In some cases the phagocytes

engulfed and destroyed the bacteria and in others the caterpillars were killed either after phagocytosis or following slight phagocytosis

Chen (45) experimentally infected fleas (*Ctenocephalides felis*) with the larvae of the tapeworm *Dipylidium caninum*. Some of the cysticercoids were destroyed by leucocytes in the coelomic cavity

13 Discussion

The mechanism of phagocytosis seems to be established as a surface energy relationship between cells and particles, such that a decrease in energy accompanies ingestion of a particle by the phagocyte. The importance of the humoral defense in rendering the particle more susceptible to engulfment by leucocytes was emphasized during a period that preceded the years covered by this review. More recently it has been recognized that the cellular defense may act in ridding the body of a bacterial infection even in the absence of circulating antibodies (sec 9a). This phenomenon of "surface phagocytosis" implies that a change in surface energy is the result of mechanical forces acting primarily on the phagocyte rather than requiring the intervention of specific immune substances. Such a demonstration serves to bring about the realization that the defense cells are subject to local modifications. There is also evidence from several sources that offers strong support to the belief that these cells may possess greater or lesser phagocytic ability under certain physiological conditions compared to those encountered in normal control animals. For example, in cases of human anemia, as well as in experimentally induced blood loss anemia in rats and mice, the blood granulocytes are more active than in controls with normal blood pictures (sec 7a). Certain nutritional deficiencies in human beings and in laboratory animals have been reported, on the other hand, to diminish the phagocytic function of the blood granulocytes (sec 6) even though all the experimental evidence on this point is not in complete agreement. Quite recently, the results of a series of experiments have shown the adrenal cortex to exert a profound effect on macrophagic activity (sec 7b) so that hypofunction or hyperfunction may accompany, respectively, adrenalectomy or the injection of adrenal cortical extract. It was also shown that chronic starvation increased the uptake of foreign particles by the spleen. While these findings were not made with leucocytes, it becomes highly suggestive that the changes induced in phagocytosis by anemia and certain types of malnutrition may be related to adrenal cortical function. Additional experiments along these lines are indicated with the possibility of explaining not only the reasons for the observed phagocytic changes that accompany these physiological stresses but also for resolving some of the contradictory results found in the literature.

The technique for studying *in vitro* phagocytosis has become essentially standardized so that quantitative results can be realized in the hands of competent investigators. It has been shown that the ratio of number of cells to number of particles is important, temperature must be accurately controlled, and agitation of the mixture should be uniform and reproducible from experiment to experiment. The nature of the test particles themselves has also been found to influence the outcome of the test, especially when bacteria are being em-

ployed Different strains of the same organism may show a wide range of susceptibility to phagocytosis and this may be explained, at least in part, by the antiphagocytic substances that seem to be produced by those organisms more resistant to ingestion by leucocytes (sec 10a and 10b) These facts should be considered in attempting to duplicate experiments This resistance to phagocytosis has been attributed in some cases to the release of negatactic substances but in others the bacteria themselves are not as readily ingested even though contacts are made Does this imply that differences in surface energy may exist in strains of a given species? Additional work is necessary to clarify this point

Closely related to this strain variation in susceptibility to phagocytosis is the difference that has been reported in the fate of ingested bacteria While in most diseases it is true that the engulfment of bacteria by phagocytic cells is tantamount to destruction, in others there is the danger of the microorganisms remaining viable within the defense cells and in this way being distributed to other parts of the body where new foci of infection may arise This is especially a potentiality in tuberculosis (sec 9b) but it also has been reported for *H. influenzae* (sec 10c) In this connection a beginning has been made in relating the period of time during which bacteria remain viable within the phagocytic cells to the action of specific immune serum Antibodies shorten the time required for the destruction of virulent *Diplo pneumoniae* with macrophages acting more rapidly in the presence of low titers than neutrophilic leucocytes Higher titers make the different cell types essentially uniform in their behavior These observations should be confirmed and extended not only for the sake of elucidating the inter-relationship between the humoral and cellular defense mechanisms but also because of their fundamental significance to general physiological principles

Changes in phagocytic functions due to chemical factors are well known, particularly in the case of normal and immune serum This opsonizing effect seems most likely to be due to two of the components of complement even though some investigators fail to concur (sec 4c) A substance like gastric mucin, on the other hand, increases the virulence of organisms by rendering them less easily phagocytized (sec 4b), while still others, some of which are therapeutic agents, are claimed to act as artificial opsonizing agents This was the case in a number of the earlier papers on the mode of action of the sulfonamides (sec 4a) so no conclusions are justified until adequate experimental verification is available At the same time, certain chemical substances, capable of lowering surface tension, may increase or decrease phagocytosis in vitro depending upon whether the primary action is, respectively, on the cells or on the particles being ingested (sec 4c (2)) All observations of this type are readily explained on the basis of theory and may be considered as offering support for its validity

There is no reason to question an intimate linkage between cells of the reticulo endothelial system and the cellular defense mechanism As evidence for this, the involvement of the spleen and liver in certain diseases, such as ma-

larial and other protozoan diseases, may be cited (sec 9d). However, there is an outstanding need for more quantitative evaluations of this activity under various experimental conditions. The use of radio-active thorium, discussed in sec 2, offers promise of achieving such results but additional work is necessary. The considerable backlog of knowledge upon which additional experiments with thorium dioxide may be based makes this the material of choice at present. However, the use of a heavy metal compound that is somewhat toxic and is unlike most materials which macrophages might be expected to ingest, raises the question as to how generally applicable the results might be. Dyes, which have been employed in evaluating macrophagic function, are also open to criticism on the grounds that they may be toxic, may diffuse into or out of cells, may be chemically altered, and, most important, yield only qualitative results. Finding a solution to these difficulties may depend upon the use of some other radio-active element which may be incorporated into a more natural type of particle for ingestion. Additional efforts along these lines are definitely indicated.

It is apparent, therefore, from the work reported in this review that man's understanding of phagocytic functions continues to expand. Much is known today but, like most aspects of body function in health and disease, the work that remains will continue to challenge the skill, patience and ingenuity of many investigators for years to come.

14 Summary

a The change in oxidative metabolism of actively phagocytosing cells increases slightly if at all. This is in agreement with the theoretical formulation of Fenn which postulates that phagocytosis is accompanied by a spontaneous decrease in free energy of surfaces. As this theory predicts, certain chemicals capable of lowering surface tension increase the ingestion of particles when applied to the leucocytes but decrease ingestion when applied to the particles. Also, the recently described "surface phagocytosis" which occurs in the absence of serum but in the presence of suitable "rough" surfaces is believed to conform to this theoretical mechanism of phagocytosis.

b Quantitative measurements of phagocytic activity are obtained by agitating a mixture of cells and particles in vitro under carefully standardized conditions and then evaluating microscopically the percent of cells showing ingestion. A new technique, based on the rate of removal of radio-active thorium, given as a colloidal suspension of thorium dioxide, has been used to determine quantitatively the activity of fixed phagocytes in vivo. Though this method has not been applied, thorium dioxide alone has been used for some years and can be made somewhat quantitative by chemical analysis of selected tissues, such as the spleen.

c Phagocytosis increases with temperature up to about 42°C . However, opsonization at 37°C gives less phagocytosis than opsonization at 22°C when the final test is performed at 37°C .

Total body x-irradiation results in a rise and subsequent return to normal

phagocytic activity of blood neutrophils, as measured *in vitro*. A second irradiation has the same effect. These observations have not been confirmed.

A linkage between the electric charge of phagocytes and particles has been reported but this continues to be problematical.

d The controversy as to whether the sulfonamides act as phagocytosis promoting agents or as bacterial inhibitors has been reviewed. These drugs are now known to be competitive inhibitors but under certain *in vitro* conditions they also seem to enhance phagocytosis. Gastric mucin, on the other hand, inhibits phagocytosis of some bacteria and renders them more virulent. Other chemical substances are also described which increase or decrease phagocytosis.

e Stored blood undergoes changes that result in a large decrease in the ability of leucocytes to ingest a wide variety of bacteria. For this reason, blood kept for more than a day or two is of little value in bolstering the cellular defense of a recipient.

f The phagocytic activity of neutrophils decreases with certain types of malnutrition but not with others. Chronic starvation increases macrophage activity. Much of this work continues to be controversial and difficult to evaluate.

g A number of factors have been reported as capable of modifying phagocytosis. Stimulation of the sympathetic nervous system increases it, adrenalectomy decreases it but injections of adrenal cortical extract increases it, leukemia decreases it, anemia, all types, increases it, and cholesterol increases it.

h The phagocytic system is of value in testing antiseptics and in the diagnosis of brucellosis. It is also a reliable means of determining the susceptibility to pertussis.

i In some diseases, phagocytosis is known to play a major role in limiting and overcoming the infection. This is especially true in pneumonia and in streptococcus infections. The sulfonamides and antibiotics hasten recovery by inhibiting bacterial reproduction but the cellular defense mechanism is ultimately responsible for the final destruction of the bacteria. This is also true, in part, of tuberculosis, protozoan diseases and certain helminthic infections. In virus infections, the role of the phagocytes is still obscure.

j Strains of the same species of bacteria may exhibit a wide range of susceptibility to phagocytosis. This is explained in some cases by the production of anti-phagocytic substances but in others the difference is a property of the bacterial cells themselves. There is also a variation in the time required for the destruction of bacteria after they are ingested into the phagocyte. Ingestion in the presence of immune serum shortens this time. The significance of these observations to the problem of resistance to disease is apparent.

k The phagocytic behavior of macrophages in such non-infectious conditions as involution of the uterus, ingestion of collagen and other breakdown products in the base of peptic ulcers, and destruction of old erythrocytes by the spleen is discussed. The nature and origin of microglia is also considered.

l The work on phagocytic function in lower animals is presented, including

that with chick embryos which are used for studying problems of bacterial infection. It is now known that the acquisition of phagocytic ability is not a gradual process but one that operates from early developmental stages

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THE COURSE OF CIRRHOSIS OF THE LIVER IN PATIENTS TREATED WITH LARGE DOSES OF LIVER EXTRACT INTRAVENOUSLY

A STUDY OF 112 CASES 44 CONTROL CASES, 68 CASES TREATED
WITH LIVER EXTRACT INTRAVENOUSLY

ELAINE P RALLI, STEPHEN H LESLIE, GEORGE H STUECK, JR.,
HAROLD E SHORR, JAMES S ROBSON, DELPHINE H CLARKE
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In a disease involving an organ with as many functions as the liver, treatment obviously cannot be confined to a single therapeutic measure. Proof of this is provided by reports of the various methods of therapy used in the treatment of cirrhosis of the liver. Beginning with the outstanding contribution of Patek in 1937 (1) in which therapy consisted of a highly nutritious diet, plus Valentine's liver extract, Vegex, and vitamin B₁, the reports of the treatment of cirrhosis have included choline, methionine, liver extract, various concentrations of all the vitamins, large amounts of dried brewers yeast, low sodium diet, mercurial diuretics, and testosterone propionate (2-11). In all of the studies not one, but a combination of several therapeutic agents has been used. This is understandable owing to the severity of the effects of the disease. It is difficult to evaluate the effectiveness of any single therapeutic measure in a disease with such widespread effect, not only are many years of observation required, but at best the outcome can only be defined as "improved", for it seems unlikely once the liver parenchyma has been replaced by fibrotic tissue that it will ever return to a completely normal state. One purpose of treatment, directed specifically to the liver, is the stimulus to regeneration of any normal remaining liver cells. Fortunately the parenchymal liver cells have an unusual capacity for regeneration (12-15) and because of this a reasonable return of function may occur in spite of the continued presence of fibrosis. Therefore substances that contain growth-promoting factors such as yeast, the fractions of the vitamin B complex, and liver extract seem particularly indicated in the treatment of the disease.

Present Study We are reporting the results of 9 years' observation on patients with cirrhosis of the liver, associated in almost all cases with a history of chronic alcoholism. The patients are divided into 2 groups. Both groups received a nutritious diet consisting of carbohydrate varying from 350-400 gms, protein ranging from 90-140 gms, and fat averaging about 120 gms. The patients in Group I received vitamin B₁, nicotinic acid, riboflavin, vitamin C, and vitamin A in large doses by mouth, intramuscularly, and, in the case of the first 4, also intravenously. Therapy with the vitamins was begun intravenously.

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This research was aided by grants from the Nutrition Foundation and the Lederle Laboratories

and continued intramuscularly until the patients were able to take the medication by mouth. In addition many of the patients in this group received a crude liver extract in doses of 5 to 10 cc. weekly, intramuscularly. The patients in Group II were treated similarly but the liver extract was given in very large doses *intravenously*. The liver extract for intravenous use was made available to us in October of 1942 by the late Dr. Charles Hoagland of the Rockefeller Institute. This extract was used until November, 1944, at which time the liver extract was provided to us by the Lederle Laboratories. In beginning therapy with liver extract intravenously, the following procedure was followed: the patient was tested for sensitivity by injecting 0.5 cc. intramuscularly. If no reaction was noted, 0.1 cc. of liver extract, diluted with 20 cc. normal saline, was given intravenously. The following day 0.5 cc. was diluted with 20 cc. normal saline. The third day the liver extract was increased to 1 cc., then to 3 cc., 5 cc., 7 cc., and 10 cc. The amount of fluid used to dilute the extract was increased proportionately so that by the time the dose was 10 cc., it was diluted with 50 cc. of either saline or 5% glucose. Using this method of procedure there have been very few untoward reactions with the liver extract. Occasionally a rise in temperature has followed if the injection was given too rapidly. Of the entire group about seven patients have had severe chills on occasion, occurring within an hour after the injection. Two patients complained of muscular cramps occurring approximately $\frac{1}{2}$ hour after the injection. The untoward effects were overcome in all but two patients by administering 10 cc. of calcium gluconate intravenously following the injection of the liver extract. In two patients intravenous administration of liver extract finally was discontinued because of the persistence of these reactions.

When we first began using liver extract intravenously, doses of 10 cc. diluted with normal saline were given 3 times a week. This dosage was continued for the first year of the study. During the second year the liver extract was increased to 15 cc., and this amount was given daily to some patients and to all patients at least 3 times a week. By the third year the weekly dose during the initial period of therapy averaged 60 cc. In the past 2 years the dose has been increased further so that at the present time the following dosage is used: during the period of active ascitic fluid reaccumulation, the patient receives 20 cc. of liver extract diluted with 80 to 200 cc. of 5% glucose, intravenously 5 to 6 times a week. This amount is continued until ascitic fluid reaccumulation is controlled. The patient then receives 20 cc. intravenously 3 times a week, and as improvement occurs the injections are reduced to twice a week and then to once a week.

Duration of Therapy Therapy with intravenously administered liver extract has been continued until the patient appeared well and until the serum proteins remained approximately normal for a period of 4 to 6 months. To achieve this state, therapy had to be continued for never less than 12 months, and most of the patients were treated for 24 months. Once the reaccumulation of ascitic fluid is controlled, the patient may leave the hospital and receive the injections 3 times weekly in the clinic.

Laboratory Determinations As we were interested in studying the course of the

disease and evaluating the response to therapy, one of the chief purposes of the laboratory determinations was to provide an objective estimate of the patient's condition. Determinations of total serum protein, albumin, globulin, total and free cholesterol, vitamin A, and carotene were done at 4- or 8-week periods. During the past 2 years gamma globulin determinations have also been done (16). During the first 5 years bromsulphalein retention tests were also done repeatedly, but as several reactions occurred this test was not done routinely. For the past 3 years the thymol turbidity test as modified by Shank and Hoagland has also been done (17, 18). Repeated protein determinations were also done on the ascitic fluid of all patients during therapy. In the past year punch biopsies have been done by Dr. J. H. Liebowitz.

TABLE I
Analysis of liver extract used and brewers yeast

	LIVER EXTRACT	BREWERS YEAST*	
		Strain G	Strain A
	per cc	mgm /gm	mgm /gm
UPS units	3.3	—	—
Total solids, mgm	178.0	—	—
Total N, mgm	14.0	—	—
Riboflavin, megm	1.2	0.075	0.040
Niacin, megm	270.0	0.500	0.400
Pantothenic acid, megm	191.0	120-160	040-060
Folic acid, megm	2.63	—	—
Pyridoxine HCl, megm	8.5	040-060	040-060
Methionine HCl, mgm	2.2	—	—
Choline Cl, mgm	11.0	—	—
Ash	—	6-7.5%	8.0%
Nitrogen free extract	—	35%	35%
Total fat	—	2.5-3.5%	1.5-2.5%
Thiamine	—	150	120

* Analysis provided by Anheuser-Busch, Inc.

Calculation of Survival. Cirrhosis of the liver in the advanced stages presented by the patients in this study provided little difficulty in diagnosis. In calculating the survival, however, it was at times difficult to arrive at a satisfactory decision as to the exact time of onset of severe liver damage, and we have therefore calculated survival from the day of admission to the hospital. On admission the patients in each group had either ascites, jaundice, or had hemorrhaged. In most cases more than one of the symptoms was present. Survival data was calculated in the manner reported by Patek (2), thus giving the opportunity for comparing our results with those he reported. Every patient in both the control and treated groups was personally cared for by 2 or more of the authors, and all of the laboratory determinations were done in the laboratories of the Department of Medicine.

Analysis of the Liver Extract. Analysis of the liver extract used has been reported (19, 20) and the values per cc of liver extract are given in Table I. It is

obvious that in view of the amounts of extract used the number of USP units was large, varying from 33 to 66 units in each injection. The vitamin content of the extract was not great compared to the amounts usually given in vitamin supplements. Even in the case of niacin and pantothenic acid, present in the greatest concentration, each cc. of liver extract only contained 270 mcgm. of niacin and 191 mcgm. of pantothenic acid. As for the lipotropic substances, methionine and choline, the amounts again were small in comparison to the known amount required to correct fatty infiltration of the liver in dogs (21). The total amount of choline contained in the larger amounts of liver extract (i.e., 20 cc.) did not exceed 0.28 gm. In the treatment of cirrhosis of the liver, the amount of choline usually given varies from 3 to 4 gm. daily. Table I also includes the analysis of dried brewers yeast. Dried brewers yeast in doses of 50 gm. daily was used by Patek (2) in the treatment of cirrhosis of the liver, and therefore it seemed to us it would be interesting to compare the concentration of the known substances in yeast with the known substances in liver extract. The analyses for both liver extract and yeast are incomplete, as there is no complete data on the number of growth-promoting factors in either of these substances. That there are growth-promoting factors in both liver extract and brewers yeast which are not accounted for by the vitamins listed in the analyses is well known (22-26). In addition extracts of liver have been reported as protective against cirrhosis produced by carbon tetrachloride or chloroform administration (27), and reports have also been made on the lipotropic effect of liver extract (28).

RESULTS

1 Control Group (Table II). The control group consisted of 44 patients of whom 30 were males. The ages varied from 24 to 71 years. The nutritional state was poor in nineteen patients, fair in six, and the remaining nineteen patients were in a good state of nutrition and some of them were even obese. Twenty-seven of the patients had jaundice. Seventeen of the patients had evidences of spider angiomas. Ascites was present in thirty-four of the patients, and this was severe enough to require paracentesis in twenty-five, or 57%. The number of paracenteses varied from one to ten per patient, and the total amount of ascitic fluid removed per patient varied from 1 to 102 liters. The serum proteins and cholesterol fractions are given for each patient on admission. The consistency of the findings shows the importance of these determinations in diagnosing cirrhosis of the liver. The average total protein was $6.0 \text{ gm \%} \pm 0.26$. The average albumin was $2.4 \text{ gm \%} \pm 0.21$. The average globulin was $3.9 \text{ gm \%} \pm 0.32$. Cholesterol determinations were done on admission, and in thirty-nine of the patients the per cent free was 30% or more. The total cholesterol varied considerably, ranging from 46 mg % to as high as 475 mg %. The level of the total cholesterol seemed to be related to the nutritional state of the individual, and the patients who were in a poor nutritional state had the very low cholesterols. As previously reported (29), we have found that the per cent free cholesterol in normal subjects varies from 29 to 22% with a mean of 26.1 and a standard

deviation of ± 1.9 . The per cent free cholesterol in patients with cirrhosis is usually above this level regardless of the level of the total cholesterol.

2 Survival Data on Control Group Survival data on the patients in Group I is shown in Table III. Calculated from the date of admission to the hospital, only 12% were surviving at the end of 3 years. Survival in this group was definitely curtailed by the end of the first year, at which time only 29% were alive, and in fact the proportion surviving dropped sharply within the first 3 months. Eight of the patients died of hemorrhage and twenty of cholemia. One patient died at home, also apparently of cholemia.

Postmortem examinations were done on twenty of the patients. The weights of the livers varied from 580 to 5000 gm. Six of the patients had large, fatty livers. Cirrhosis of the liver was present in all of the subjects and in two was complicated by liver cell carcinoma.

3 Admission Data on Group Treated with Liver Extract Intravenously (Group II), Table IV This group consisted of sixty-eight patients of whom forty-eight were males. The ages varied from 11 to 78 years. The nutritional state was poor in twenty-three patients, fair in twenty, and good in the remaining twenty-five patients. Thirty-five of the patients were jaundiced on admission and twenty-eight had spider angiomas. Sixty-five of the patients had ascites. In fifty (74%) the ascites was severe enough to require paracentesis. The number of paracenteses sustained by individual patients varied from 1 to 46. In several patients ascites was controlled after as many as 24 paracenteses. The amounts of ascitic fluid removed were considerable, as is shown in the table. In the severe cases over 300 liters of ascitic fluid were removed during the course of therapy. One patient who is alive today, 6 years from the time of therapy, had 370 liters of fluid removed during the course of the disease. Another patient who is alive today, 3 years after therapy, had 321 liters of fluid removed.

Table V gives a summary of the findings on both groups. The average total protein in the "liver extract treated" group was $6.1 \text{ gm \%} \pm 0.25$, the average albumin was $2.4 \text{ gm \%} \pm 0.18$, the average globulin was $3.7 \text{ gm \%} \pm 0.25$. Obviously from the point of view of the serum proteins the 2 groups were very similar. Cholesterol determinations were also done on all cases on admission in this group. In six patients the per cent free cholesterol was below 30%, but in only one case was it within normal limits. The variations in the total cholesterol were similar to those of the control group and the very low values were associated with malnutrition.

4 Survival Data on Group II Table VI gives the survival data calculated from the date of admission to the hospital. In this group enough patients survived so that survival could be calculated for 5 years (60 months). At the end of 5 years, 41% of the patients were alive. The comparison with the control group is best shown graphically (Figure 1). It was an interesting fact that none of the patients in Group II died within the first 2 months of treatment. By the end of the 3rd month 92.6% were still alive, and by the end of the 5th month 84.5% were still alive, whereas in the control group at the end of the 5th month

TABLE II
Data on group I—patients treated in conventional manner

CASE NUMBER	AGE	SEX	NUTRITIONAL STATE	JAUNDICE	ANGIO-MATA	ASCITES AND DURATION PRIOR TO ADMISSION	# PARACENTASES DURING COURSE OF DISEASE	TOTAL VOL- UME ASCITIC FLUID RE- MOVED, LITERS	PROTEINS GM %			KOR N	CHOLESTEROL MGM %			CAUSE OF DEATH	WEIGHTS OF LIVER gms
									Total	Albu- min	Glob- ulin		Total	Free	% Free		
1C	50	M	Good	Y	N	2½ wk	1	5.5	3.7	2.0	1.7	32	310	301	97	Cholemia	2990
2C	47	M	Obese	Y	N	4 da	1	6.0	4.7	2.2	2.5	75	121	117	97	Cholemia	4000
3C	49	F	Poor	N	N	2 wk	1	2.7	—	—	—	30	46	38	83	Cholemia	1600
4C	24	F	Poor	Y	Y	8 mo	2	10.0	—	—	—	33	194	113	60	Cholemia	1700
5C	39	F	Poor	N	N	9 mo	1	0.6	7.1	3.0	4.1	30	114	55	48	Cholemia	1150
6C	71	F	Poor	Y	N	4 mo	None	None	6.1	2.2	3.9	32	109	58	53	Cholemia	940
7C	40	M	Obese	Y	Y	1 mo	2	9.0	6.7	2.7	4.0	32	150	128	85	Cholemia	4000
8C	50	M	Obese	Slight	Y	?	None	None	—	—	—	31	83	47	57	Hemorrhage	3070
9C	52	M	Poor	Y	N	12 mo	2	22.0	6.3	1.9	4.4	30	82	53	65	Cholemia	1320
10C	61	M	Fair	N	N	1 mo	3	30.0	7.2	3.0	4.2	34	162	77	48	Hemorrhage	1340
11C	49	M	Fair	N	Y	On Adm	None	None	7.2	3.2	4.0	66	314	234	75	Hemorrhage	3800
12C	45	M	Poor	Y	N	2 wk	4	20.0	7.1	2.7	4.4	24	125	85	68	Hemorrhage	1450
13C	45	F	Poor	Y	N	?	None	None	5.5	2.5	3.0	19	318	284	89	Cholemia	5000
14C	50	F	Poor	Slight	N	6 wk	1	8.0	6.7	1.7	5.0	16	165	72	44	Hemorrhage	1100
15C	35	F	Poor	N	N	4 wk	2	1.8	6.5	1.8	4.7	32	127	40	31	Cholemia	Small
16C	60	M	Good	Y	N	@12 mo	2	14.0	6.2	1.9	4.3	43	200	81	41	Cholemia	2200
17C	56	F	Poor	N	N	6 wk	3	38.5	6.0	2.2	3.8	23	182	67	37	—	—
18C	55	F	Fair	Slight	N	8 mo	7	48.0	7.1	1.6	5.5	53	—	—	—	Cholemia	—
19C	40	M	Good	N	Y	8 mo	10	102.5	6.1	2.2	3.9	32	167	54	32	Cholemia	—
20C	49	M	Fair	Y	Y	2 wk	1	9.0	6.6	2.4	4.2	38	142	105	74	Hemorrhage	—
21C	39	M	Poor	Y	Y	3 mo	1	7.6	7.2	2.7	4.5	36	194	103	53	Hemorrhage	1920
22C	36	F	Poor	Y	Y	2 wk	None	None	3.9	1.7	2.2	—	—	—	—	Cholemia	—
23C	48	M	Obese	Y	Y	@2 wk	1	12.0	6.2	2.4	3.8	39	200	122	61	Cholemia	—
24C	47	M	Poor	Y	Y	5 mo	5	45.0	5.5	1.3	4.2	26	151	64	42	—	—
25C	61	M	Poor	N	N	5 wk	5	43.0	5.7	2.8	2.9	—	—	—	—	Cholemia	580
26C	53	M	Good	Slight	Y	3 mo	None	None	6.2	3.2	3.0	30	—	—	—	—	—

27C	58	F	Good	N	Y	None	None	0 0	1 8	4 2	72	—	—	—	Cholemia	1320
28C	56	M	Poor	N	N	6 mo	1	5 5	1 7	3 8	31	69	10	—	Hemorrhage	1240
29C	57	F	Obese	Slight	Y	4 wk	10*	6 3	1 8	4 5	30	51	39	—	Cholemia	—
30C	38	F	Poor	N	Y	6 mo.	1	6 9	1 6	5 3	34	26	36	—	—	—
31C	39	M	Poor	Y	Y	1 wk	4	6 6	3 5	3 1	39	211	107	50	Cholemia	—
32C	38	M	Poor	N	N	6 wk	3	5 3	3 3	2 0	35	178	58	33	Cholemia	—
33C	43	M	Good	N	N	None	None	5 4	2 4	3 0	28	203	64	31	—	—
34C	37	M	Fair	N	N	?	None	6 0	2 6	3 4	37	112	39	36	—	—
35C	42	M	Good	Y	Y	None	None	6 4	3 2	3 2	19	149	15	30	—	—
36C	40	M	Good	Y	Y	None	None	6 3	4 8	1 5	37	389	117	30	—	—
37C	61	F	Poor	Slight	N	?	None	5 9	2 8	3 1	21	218	82	38	—	—
38C	59	M	Good	N	Y	1 wk	None	4 8	2 9	1 9	38	219	109	50	—	—
39C	49	M	Good	Y	Y	2 wk	None	5 1	1 6	3 5	21	305	296	97	—	—
40C	52	M	Fair	N	N	?	None	6 3	2 0	4 3	26	128	50	39	—	—
41C	39	M	Good	N	N	3 wk	None	5 5	2 8	2 7	40	132	34	26	—	—
42C	60	M	Good	Y	Y	None	None	5 7	2 4	3 3	27	193	68	35	—	—
43C	59	M	Good	Y	Y	None	None	6 0	2 3	3 7	25	475	420	88	—	—
44C	40	M	Good	Y	Y	10 wk	None	5 7	1 8	3 9	22	265	95	36	—	—

* Including 5 thoracenteses, volume 10 liters

only 37.5% were alive. After 3 years, 48% of the treated group were alive, as compared to 12% of the control group. Of the thirty patients dying in this group, ten died of hemorrhage and the rest of cholemia. Postmortem examinations were done on fourteen patients. Cirrhosis of the liver was found in every case. The size of the liver varied from 735 to 3260 gm. One of the patients on whom a postmortem examination was done also had a liver cell carcinoma, and it was our impression that one patient on whom we were unable to do a postmortem might also have had an associated liver cell carcinoma.

We are able to compare these data to Dr. Patek's group observed for a similar

TABLE III

Group I—control—conventionally treated

Survival from date of admission to the hospital

PERIOD (AT END OF MONTH)	NUMBER OBSERVED AT BEGINNING OF PERIOD A	DIED DURING PERIOD B	DROPPED FROM OBSERVATION DURING PERIOD C	PROPORTION DYING DURING PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD (q) $D = B/A$	PROPORTION LIVING AT END OF PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD $(p = 1 - q)$ $E = 1 - D$	PROPORTION SURVIVING AT END OF PERIOD OF ORIGINAL COHORT (1) F
1st month	44	13	0	295	705	705
2nd month	31	5	4	161	839	592
3rd month	22	3	4	136	864	511
4th month	15	3	0	200	800	409
5th month	12	1	2	083	917	375
6th month	9	1	0	111	889	333
7th month	8	1	0	125	875	291
8th month	7	0	0	000	1 000	291
9th month	7	0	0	000	1 000	291
10th month	7	0	1	000	1 000	291
11th month	6	0	0	000	1 000	291
12th month	6	0	0	000	1 000	291
15th month	6	1	0	167	833	243
18th month	5	0	1	000	1 000	243
21st month	4	0	2	000	1 000	243
24th month	2	0	0	000	1 000	243
30th month	2	0	0	000	1 000	243
36th month	2	1	1	500	500	122

length of time, although survival in his group is calculated from the onset of ascites (30). In addition to a highly nutritious diet of 140 gm. protein (which included the protein in dried brewers yeast), 365 gm. carbohydrate, and 175 gm. fat, a total of about 3500 calories, he gave brewers yeast (50 gm. daily), vitamin B₁, nicotinic acid, and riboflavin. Some of his patients also received choline, otheis methionine, and in six patients liver extract intravenously. However, the weekly dose, except in one case was only 37 cc. At the end of 5 years, 30% of his treated group survived, whereas in our treated group, calculated from admission to the hospital, at the end of 5 years 41% had survived.

5 *Dose and Duration of Therapy with Liver Extract Intravenously.* As men-

tioned previously, after the first year the amounts of liver extract given intravenously were increased to 45 cc weekly, then to 60 cc weekly, and finally to 100-120 cc weekly. The total amounts of liver extract administered varied from 100 cc to 5000 cc per patient. The total period of time over which patients received liver extract intravenously varied from 1 month to 3½ years. It has seemed to us that the amounts of liver extract given weekly, particularly in the first 2 months of therapy, influenced the course of the disease as evidenced by the reaccumulation of ascitic fluid and the response of the serum proteins. The effects of therapy with varying doses of liver extract are illustrated in the charts. Figures 2, 3 and 4 show the course of the disease in patients treated initially with doses of 30 to 60 cc weekly, and Figure 5 shows the course in a patient treated with doses of 100 to 120 cc weekly.

Case 24 (Figure 2) was admitted to the hospital in May of 1946. He gave a history of protrusion of the abdomen for a year and of slight jaundice for 6 months. The first paracentesis was done in January of 1946 at another hospital, where he was treated with mercurial diuretics, vitamins, and a high-protein diet. He required numerous paracenteses and was transferred to Bellevue Hospital on May 31, 1946. He was begun on liver extract intravenously on June 6, and his course and the amounts of liver extract are shown in the chart. He improved sufficiently to be discharged from the hospital on October 15, 1946, and went back to work. A paracentesis was done on January 2, 1947, to measure the amount of ascitic fluid present in the abdomen. Only 2000 cc were obtained. He had a small amount of ascites during the next 4 months, and he was tapped on April 24, 1947, again to determine the amount of ascitic fluid present. At this tap only 1000 cc were obtained. Following this there was no evidence of ascites, and liver extract therapy was stopped at the 12th month. The latest blood chemistry, done in November, 1948, showed a total protein 7.2 gm %, albumin 4.5 gm %, globulin 2.7 gm %, NPN 43 mgm %, total cholesterol 256 mg %, free cholesterol 69 mg %, per cent free 27%, thymol turbidity 8.5 units.

Case 28 (Figure 3) was admitted to the hospital in March, 1947. He received approximately 200 cc of liver extract intravenously per month for the first 4 months, and ascites was well enough controlled at this time for him to be discharged from the hospital. Two more paracenteses were done from the 5th to the 7th months and because the albumin levels were still low and the per cent free cholesterol remained above normal, the amounts of liver extract were increased and the patient received monthly approximately 250 cc for the following 4 months. This patient now receives only one injection a week, the blood chemistries are within normal limits, and there has been no evidence of ascites since the last tap.

The next case, Case 61 (Figure 4), was admitted to Bellevue Hospital in May of 1947 and liver extract was begun in June of 1947. The patient at first received approximately 50 cc a week and was gradually built up to a larger dose. Reaccumulation of ascitic fluid was controlled during the 5th month. The last paracentesis was done in October of 1947, the patient is alive and well today and is now receiving liver extract only once a week.

TABLE IV
Data on group II—patients treated with liver extract intravenously

CASE NUMBER	AGE SEX	NUTRI- TIONAL STATE	JAUNDICE	AN- GIO- MATA	ASCITES AND DURATION PRIOR TO ADMISSION	% PARA- CENTESES DURING COURSE OF DIS- EASE	TOTAL VOL- UME FLUID REMOVED	PROTEINS GM %			% N, N ₂ , KGM %	CHOLESTEROL MG% %			DURA- TION EX- TRACT THER- APY	TOTAL AMOUNT LIVER EX- TRACT GIVEN I V	CAUSE OF DEATH	WT gm
							liters	Total	Albu- min	Glob- ulin		Total	Free	% Free	months	cc		
1	49 M	Poor	Slight	Y	6 mo	8	73	6.5	2.5	4.0	37	131	41	31	12	4996	—	—
2	45 M	Obese	N	N	On adm	None	None	6.5	3.8	2.7	41	185	51	28	6	660	—	—
3	62 M	Poor	N	N	4 mo	41	292	6.7	2.7	4.0	25	141	48	34	9	900	Cholemia	735
4	46 M	Poor	Slight	N	6 wk	5	45	6.2	2.6	3.6	35	149	84	56	6	1375	—	—
5	56 M	Fair	Y	N	2 mo	6	52	6.8	2.3	4.5	23	198	91	46	2	230	Cholemia	2900
6	49 M	Good	Y	Y	7 mo	1	4	5.6	2.0	3.6	24	120	46	38	2	196	Cholemia	—
7	56 M	Good	N	N	3 mo	4	27	5.5	2.2	3.3	30	150	60	40	3	452	—	—
8	53 M	Obese	N	Y	On adm	None	None	6.7	3.4	3.3	49	190	70	36	2	452	—	—
9	50 M	Fair	Y	Y	3 wk	7	65	5.2	2.6	2.6	29	114	39	35	3	1195	Cholemia	1270
10	58 M	Good	Y	N	1 mo	8*	81	4.7	1.4	3.3	23	101	39	38	6	2000	Chol + cardiac	—
11	67 F	Poor	N	N	9 mo	19	102	6.8	2.9	3.9	18	126	45	36	20	900	Cholemia	—
12	45 M	Fair	N	N	3 wk	None	None	6.7	3.4	3.3	25	180	55	31	1	155	—	—
13	40 M	Good	N	N	2 mo	None	None	6.5	2.4	4.1	26	200	93	46	33	2254	—	—
14	47 F	Fair	N	Y	9 mo	34	370	5.6	2.4	3.2	30	169	57	33	37	2400	—	—
15	78 M	Good	Y	N	3 wk	6	49	6.1	1.6	4.5	41	104	36	35	6	509	Cholemia	—
16	45 M	Good	N	N	1 mo	None	None	6.5	3.4	3.1	23	127	34	27	12	490	—	—
17	42 M	Good	Y	Y	SI on adm	None	None	7.0	3.4	3.6	33	321	115	37	11	3340	—	—
18	46 M	Good	N	Y	18 mo	20	272	6.1	2.1	4.0	32	112	45	40	27	1657	Chol + cardiac	1370
19	67 M	Poor	N	N	10 da	7	65	5.0	2.0	3.0	31	128	43	33	3	75	Hemorrhage	1100
20	57 M	Poor	Y	Y	5 mo	8	84	6.7	1.8	4.9	57	119	42	35	3	224	Cholemia	—
21	11 F	Fair	Slight	N	8 mo	None	None	5.7	2.6	3.1	29	105	40	38	38	125 ^a	—	—
22	70 M	Poor	N	N	8 ¹ mo	16	153+	5.3	2.3	3.0	35	195	57	29	5	460	Chol + Infec	920
23	42 M	Obese	Y	Y	3 wk	None	None	7.5	2.7	4.8	28	255	148	58	21	1718	—	—
24	52 M	Poor	N	Y	5 mo	46	321	5.8	2.2	3.6	25	132	43	31	12	1081	—	—
25	42 F	Poor	N	Y	9 mo	25	295	6.6	2.7	3.9	37	155	57	36	21	1989	Cholemia	—
26	48 F	Poor	N	N	6 da	None	None	6.1	2.9	3.2	32	167	55	33	1	65	Cholemia	—

27	35	F	Poor	Y	Y	3 mo	3	30	5 0	3 4	4 6	31	168	62	36	24	1780	—	—
28	46	M	Poor	N	N	5 mo	14	133	8 0	2 5	2 5	4 9	165	59	35	20	3514	—	—
29	49	M	Fair	N	N	2 mo	4	26	6 8	1 9	4 9	21	179	66	37	9	502	Hemorrhage	2570
30	39	F	Fair	Y	Y	4 mo	4	7	6 6	2 2	4 4	27	130	62	48	27	150 ^b	Hemorrhage	—
31	43	M	Fair	N	N	On adm	13	108	6 3	2 5	3 8	22	117	34	29	5	593	Hemorrhage	—
32	51	M	Fair	Y	Y	On adm	2	8	5 3	2 7	2 6	33	107	60	56	7	2400	—	—
33	57	M	Fair	Slight	Y	On adm	13	146	5 3	1 5	3 8	33	161	63	42	3	277	Hemorrhage	—
34	43	M	Good	Y	Y	7 wk	12	69	7 8	2 1	5 7	23	124	51	41	31	1850	Hemor + ehof	1460
35	48	F	Fair	Y	Y	5 1/2 mo	23	216	5 8	2 7	3 1	25	190	58	30	4	320	Chol + infec	1600
36	31	M	Good	Y	Y	7 mo	1	1	4 4	1 4	3 0	33	244	121	49	2	210	Cholema†	3260
37	64	M	Obese	Y	Y	6 wk	12	119	5 7	2 4	3 3	21	130	52	40	2	180	Cholema	1260
38	64	M	Poor	N	N	5 mo	29	326	4 7	2 3	2 4	35	142	49	35	10	4265	Cholema	1100
39	56	F	Poor	N	N	1 mo	12	67	5 6	1 4	4 2	31	163	71	42	3	155	Chol + infec	980
40	37	F	Obeso	Slight	Y	On adm	8	96	5 9	1 9	4 0	28	200	79	39	1	45	—	—
41	57	M	Good	N	N	4 mo	Nono	Nono	5 9	2 8	3 1	23	119	35	29	4	90	Hemorrhage	—
42	60	M	Fair	N	N	2 wk	14	233	6 5	1 9	4 6	23	184	67	35	6	720	Cholema	—
43	51	F	Good	Y	Y	2 wk	8	21	6 6	2 6	4 0	42	107	—	—	12	2300	—	—
44	37	M	Poor	N	N	5 mo	9	96	6 6	2 7	3 9	22	145	63	11	1	4930	Hemor + ehof	—
45	53	M	Obese	Slight	Y	3 mo	3	26	6 3	1 9	4 4	36	152	76	71	3	112	Cholema	—
46	43	M	Fair	Y	N	On adm	2	3	5 0	2 8	2 2	35	102	78	33	5	290	—	—
47	59	M	Good	Y	N	10 da	1	7	5 4	1 8	3 6	28	206	100	35	7	370	—	—
48	42	M	Poor	Y	Y	None	Nono	Nono	8 1	2 7	5 4	29	288	100	35	7	1700	—	—
49	33	M	Fair	Y	Y	12 da	Nono	Nono	6 8	2 4	4 4	22	194	74	33	10	380	—	—
50	54	M	Obese	N	N	5 wk	36	395	5 8	2 1	3 7	28	145	55	38	25	2685	Cholema	—
51	66	M	Poor	N	N	10 da	2	17	5 6	1 7	3 9	31	127	41	32	5	220 ^c	—	—
52	47	F	Good	N	Y	1 mo	Nono	Nono	5 6	3 1	2 5	24	198	66	33	10	715 ^a	—	—
53	36	F	Fair	N	N	On adm	1	4	6 2	1 5	4 7	30	161	70	43	3	160	—	—
54	66	F	Fair	Slight	Y	2 wk	5	27	5 0	2 9	2 1	21	135	89	66	5	783	—	—
55	72	M	Fair	N	N	1 wk	1	Unknown	6 3	2 4	3 9	29	94	31	33	21	1580	—	—

* Case No 10 had in addition 4 thoracenteses, total volume 4625 cc

† Case No 36 also had agranulocytosis

TABLE IV—Continued

CASE NUMBER	AGE	SEX	NUTRI- TIONAL STATE	JAUNDICE	AN- GIO- MATA	ASCITES AND DURATION PRIOR TO ADMISSION	% PARA- CENTESIS DURING COURSE OF DIS- EASE	TOTAL VOL- UME ASCITIC FLUID RE- MOVED	PROTEINS GM %			NPN, MGR %	CHOLESTEROL MGM %			DURA- TION LIVER EX- TRACT THER- APY	TOTAL AMOUNT LIVER EX- TRACT GIVEN IV	CAUSE OF DEATH	gm
								liters	Total	Albu- min	Glob- ulin		Total	Free	% Free	months	cc		
56	49	M	Fair	Y	Y	1 mo	5	31	5.5	2.5	3.0	37	119	51	42	2	869	Hemorrhage	—
57	51	F	Poor	Y	N	3 da	None	None	5.6	2.3	3.3	26	110	79	71	2	1020	Hemorrhage	1275
58	52	M	Poor	Y	N	6 mo	1	3	6.2	1.6	4.6	23	193	74	38	3	196	—	—
59	47	F	Poor	N	Y	3 mo	8	64	5.6	2.4	3.2	35	77	31	40	4	1812	—	—
60	36	M	Good	N	N	None?	None	None	6.9	3.6	3.3	44	151	36	24	8	790	—	—
61	42	M	Poor	Y	N	2 mo	13	101	4.9	2.2	2.7	50	144	44	31	17	3675	—	—
62	26	F	Poor	Y	N	None	None	None	7.6	2.7	4.9	42	77	34	45	2	530	—	—
63	45	M	Good	Y	N	2 wk	None	None	5.5	3.4	2.1	31	327	120	37	4	785	—	—
64	36	F	Fair	Y	Y	1 yr	3	Unknown	6.2	1.7	4.5	35	118	61	52	2	140	—	—
65	41	M	Poor	N	Y	2 mo	3	16	6.0	2.1	3.9	30	—	—	—	2	880	Hemorrhage	1120
66	43	F	Good	N	N	5 mo	None	None	5.6	2.3	3.3	29	171	78	46	8	365	—	—
67	42	M	Poor	Y	N	1 mo	3	28	7.1	2.8	4.3	31	215	68	31	3	1400	—	—
68	42	F	Fair	Slight	N	8 mo	4	35	6.9	1.6	5.3	28	132	53	44	4	205	—	—

^a In addition Case No 21 received 770 cc liver extract intramuscularly^b In addition Case No 30 received 670 cc liver extract intramuscularly^{c,d} Cases No 51 and 52 received an additional 390 cc of liver extract intramuscularly

The next case, Case 1 (Figure 5), was admitted in October, 1947, and received 100-120 cc of liver extract weekly from the onset of therapy. In this patient the reaccumulation of ascitic fluid was controlled by the end of the 4th month. The patient had a very large umbilical hernia which was operated on while he was in the hospital, and he was continued on the large doses of liver extract until September, 1948. He is now receiving 40 cc a week and appears well.

The group of patients treated with the larger doses of liver extract from the onset of therapy is not large, but it is our impression that the period of reaccumu-

TABLE V
Summary of findings in both groups

	GROUP I—CONTROL		GROUP II—LIVER EXTRACT INTRAVENOUSLY	
	Number of patients			
	44		63	
	Range of ages			
	21-41 yrs		41-73 yrs	
	Number	Per cent	Number	Per cent
Females	14	31.8%	20	29.5%
Males	30	68.2%	43	70.5%
Nutritional state				
Poor	19	43.5%	23	33.8%
Fair	6	13.4%	20	23.4%
Good	19	43.3%	20	36.8%
Jaundice	17	61.4%	33	51.3%
Angiomata	17	38.6%	28	41.2%
Ascites	42	94.4%	63	95.6%
Ascites requiring paracentesis	13	36.8%	50	77.5%
Dead	13	65%	30	42%
Mean total protein, gm %	6.0 = .25		6.1 = .25	
Mean albumin, gm %	2.7 = .11		2.8 = .18	
Mean globulin, gm %	3.3 = .25		3.3 = .25	

lation of ascitic fluid has been so rapid and that a more rapid increase in the level of serum albumin has occurred. Several patients receiving massive doses of liver extract have died during the course of therapy, one in apparent heart failure, two from hemorrhage and one from pneumonia. With one exception all these patients survived for 3 months from admission to the hospital.

6 Serum Values for Protein. In Table VI are shown the serum protein, albumin, globulin, cholesterol, vitamin A and vitamin E values for four of the patients (Cases 51, 44, 14, and 15) before and after therapy. Similar determinations were done on every patient before and after therapy. The results are given in the table.

of the changes occurring during the course of the disease Examination of these data make it clear that the response to therapy is associated with a very slow increase in the level of serum albumin and in most of the patients it was months before any striking improvement was detected. The examples cited in this table also serve to illustrate the constancy of the derangement in the cholesterol fractions The per cent free cholesterol was above the normal limits in each case

TABLE VI

Group II—treated with liver extract intravenously

Survival from date of admission to hospital

PERIOD (AT END OF MONTH)	NUMBER OBSERVED AT BEGINNING OF PERIOD A	DIED DURING PERIOD B	DROPPED FROM OBSERVATION DURING PERIOD C	PROPORTION DYING DURING PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD (q) $D = B/A$	PROPORTION LIVING AT END OF PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD $(p = 1 - q)$ $E = 1 - D$	PROPORTION SURVIVING AT END OF PERIOD OF ORIGINAL COHORT (1) F
1st month	68	0	0	000	1 000	1 000
2nd month	68	0	0	.000	1 000	1 000
3rd month	68	5	1	.074	926	926
4th month	62	3	2	.048	.952	891
5th month	57	3	1	.052	948	845
6th month	53	3	2	.057	943	797
7th month	48	3	3	.063	937	747
8th month	42	0	1	.000	1 000	747
9th month	41	1	1	.024	976	729
10th month	39	1	0	.026	974	710
11th month	38	2	2	.053	947	672
12th month	34	1	2	.029	971	653
15th month	31	0	2	.000	1 000	653
18th month	29	0	2	.000	1 000	653
21st month	27	0	3	.000	1 000	653
24th month	24	1	1	.042	958	626
30th month	22	3	1	.136	864	541
36th month	18	2	5	.111	889	481
42nd month	11	0	4	.000	1 000	481
48th month	7	1	1	.143	857	412
54th month	5	0	1	.000	1 000	412
60th month	4	0	1	.000	1 000	412

In the treatment of patients with cirrhosis of the liver in this study we have found that the per cent free cholesterol was usually the first serum determination to give any evidence of improvement

The plasma levels of vitamin A were low in almost every patient on admission. The range was from 0.6 to 36 mcgm % and in only 2 cases was the vitamin A above 28 mcgm %. We have found the mean level of vitamin A in normal subjects to be 43 mcgm % ± 12 . The plasma carotene levels varied considerably in the patients (30 mcgm % to 216 mcgm %). The values were mostly on the low side of normal and were lowest in the patients who were malnourished

In this respect the serum carotene was similar to the total cholesterol level. Following therapy the plasma vitamin A rose, particularly if vitamin A was administered. Administration by mouth was more successful than intramuscular injection. The observation of the low level of vitamin A corroborates previous observations (34, 35) of a disturbance in the metabolism of vitamin A in patients with cirrhosis of the liver.

7 *Concentration of Protein in the Ascitic Fluid* Total protein, albumin, and

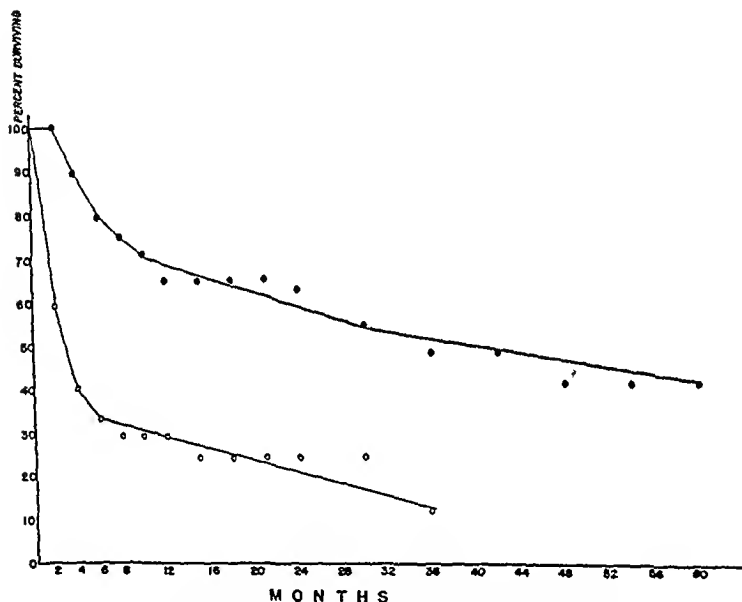


FIG 1 COMPARISON OF SURVIVAL IN THE TWO GROUPS

Solid circles patients treated with liver extract intravenously, clear circles patients treated in the conventional manner

globulin determinations were done on the ascitic fluids in most of the patients, and in many of the cases repeated determinations were done during the course of therapy. On admission, in twenty-nine patients, the average total protein of the ascitic fluid was $1.2 \text{ gm \%} \pm 0.18$, the albumin was $0.70 \text{ gm \%} \pm 0.12$, and the globulin was $0.50 \text{ gm \%} \pm 0.11$. In the majority of the patients repeated determinations during the course of the disease showed no significant changes in the concentration of total protein, albumin, or globulin in the ascitic fluid. The amounts of ascitic fluid removed from the patients were great, so that considerable amounts of protein were lost to the body in this way. For example, in Case

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2nd month	68	0	0	.000	1.000	1.000
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5th month	57	3	1	.052	.948	.845
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10th month	39	1	0	.026	.974	.710
11th month	38	2	2	.053	.947	.672
12th month	34	1	2	.029	.971	.653
15th month	31	0	2	.000	1.000	.653
18th month	29	0	2	.000	1.000	.653
21st month	27	0	3	.000	1.000	.653
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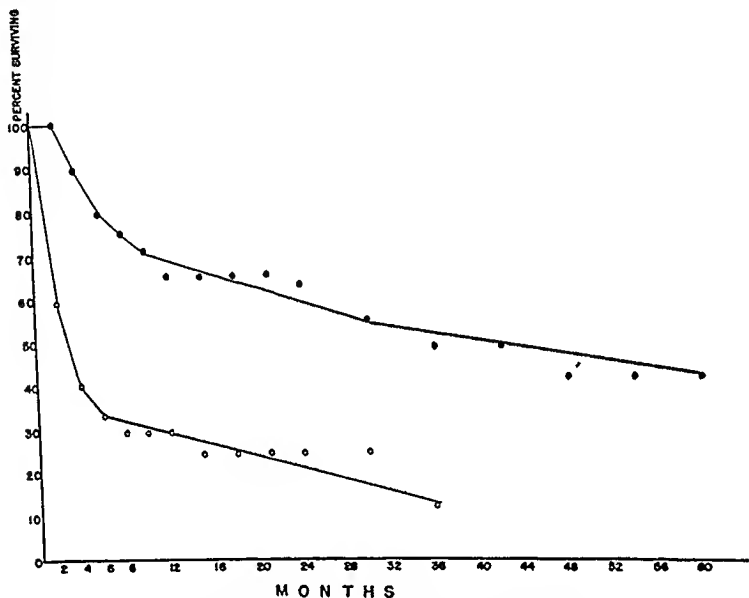


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Solid circles patients treated with liver extract intravenously, clear circles patients treated in the conventional manner

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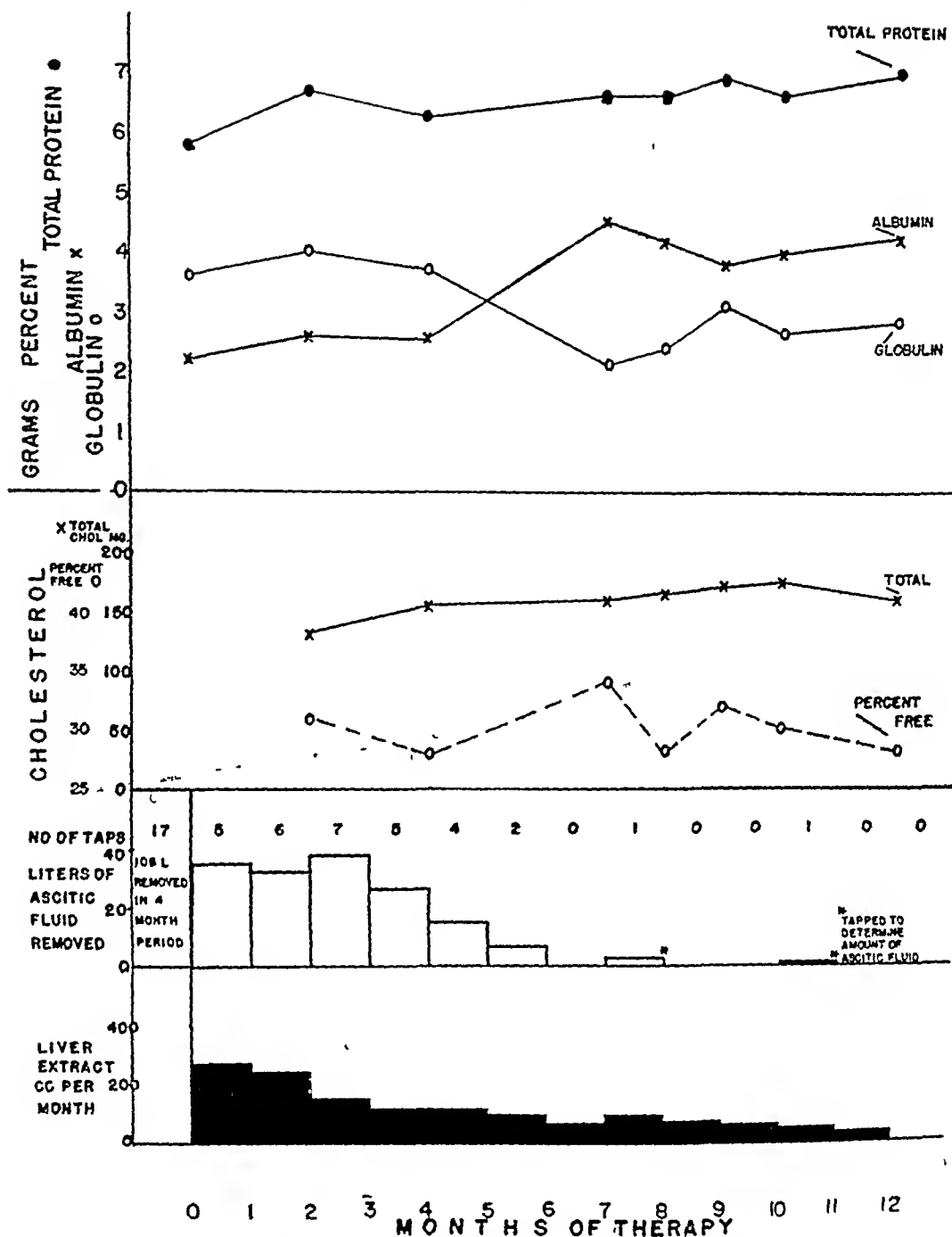


FIG 2 COURSE OF THE DISEASE IN CASE No 24

The patient, a 52-year-old white male, was admitted to the hospital May 31, 1946. He had been treated previously in another hospital and had had 17 paracenteses. On admission he appeared chronically ill, malnourished, and had a low albumin level, 2.2 gms %. During the first 4 months in the hospital he had a total of 27 paracenteses. In the 5th month he required 2 paracenteses. He was then discharged from the hospital. In the 7th month a paracentesis was done solely for the purpose of ascertaining how much fluid was in the abdomen and 3000 cc of fluid were removed. Very little fluid reaccumulated after this, and in order to check the validity of the observations another paracentesis was done in the 10th month and only 700 cc of fluid were found in the abdomen. This patient is alive and well today.

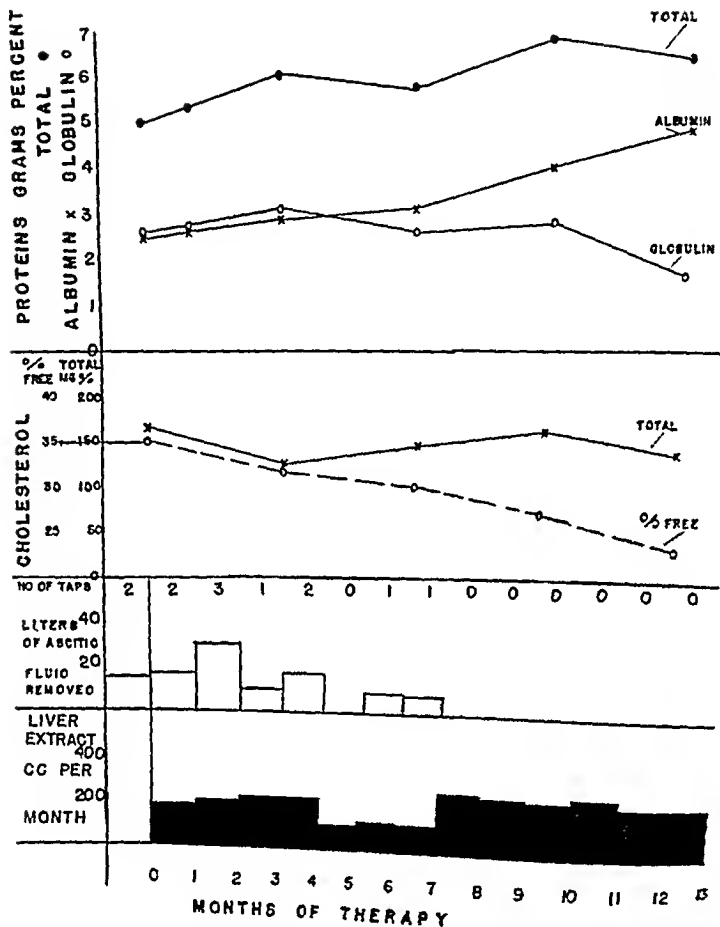


FIG 3 COURSE OF THE DISEASE IN CASE No. 23

The patient, a 46 year old white male, was admitted to the Lenox Hill Hospital on March 11, 1947, with massive ascites and anasarca. The ascites was moderately controlled by the 4th month and the patient was allowed to go home and be followed out-patient. The ascites recurred again in the 5th and 6th months. The amounts of liver extract administered from the 4th to the 7th months, but were increased again at this time because that the albumin level was still not within normal limits. The patient is today, entirely free of ascitic fluid, with normal blood chemistries.

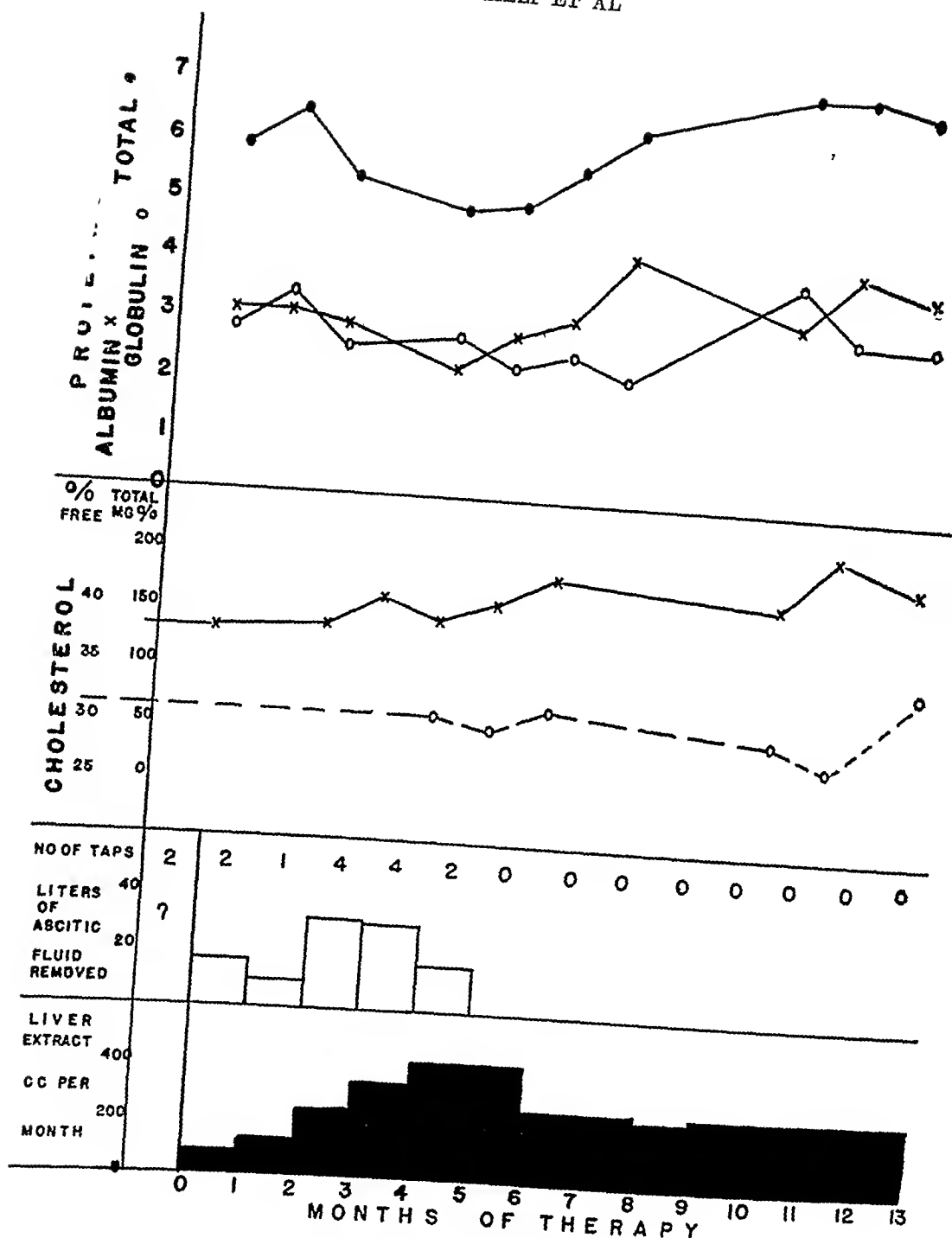


FIG 4 COURSE OF THE DISEASE IN CASE No 61

The patient, a 42-year-old male, was admitted to the hospital on May 22, 1947. The ascites was controlled by the 5th month. The liver extract was increased gradually so that during the 4th and 5th months he received a little over 400 cc monthly. As reaccumulation of ascitic fluid decreased, the albumin fraction in the serum rose and reached a normal level in the 7th month. The amounts of liver extract were decreased and the patient was treated in the clinic. He is alive and well.

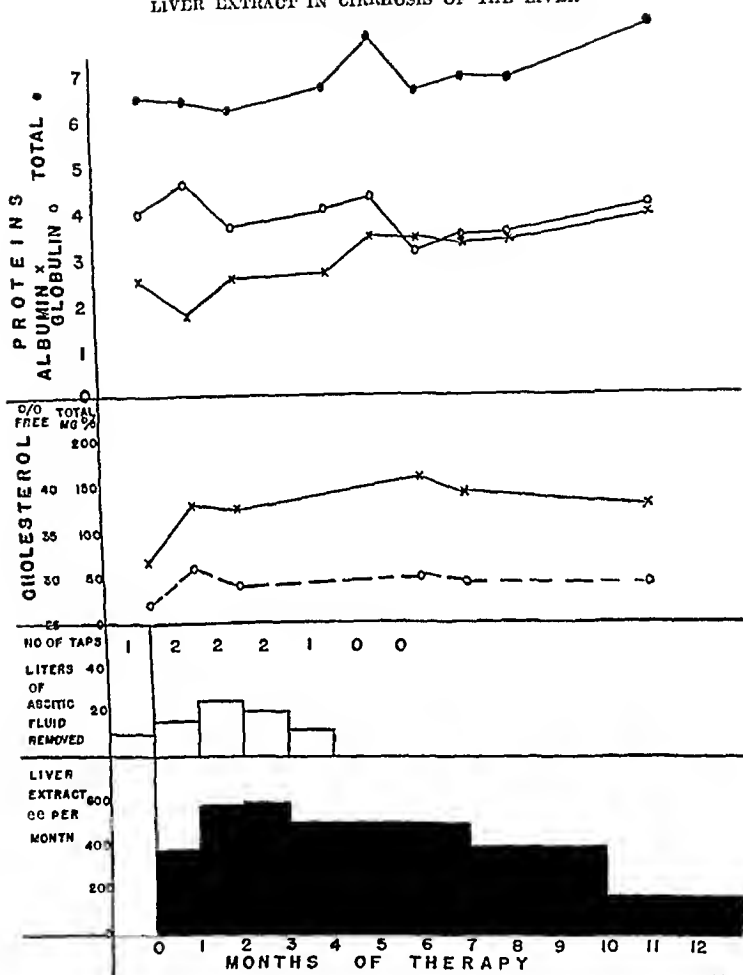


FIG 5 COURSE OF THE DISEASE IN CASE No 1

The patient, a 49 year old male, was admitted on October 22, 1947, with a history of abdominal swelling of 6 months duration, weakness and fatigue for 1½ months. The patient was a poorly nourished man, the sclerae were slightly icteric, there were numerous spider angiomata over the upper trunk, the abdomen was distended with fluid. The liver and spleen were both enlarged and there was 3+ edema of the ankles. As is shown in the chart, the patient had 8 paracenteses, the last one was done February 7, 1948. The patient is alive and well.

TABLE VII
Serum protein, cholesterol, vitamin A*, and carotene* values during course of therapy with intravenous liver extract

	DE- FORE- THER- APY	MONTHS OF THERAPY																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case #51																				
Tot prot, gm %	56	57†	72	68	81	77		70	67	61	—	62	66		70	65		70		
Albumin, gm %	17	17	2.5	2.6	3.4	3.4		33	30	32	—	34	34		36	34		36		
Globulin, gm %	39	40	47	42	47	43		37	37	29	—	28	32		34	31		34		
Tot chol, mg %	127	111	124	135	138	150		185	175	188	—	188	190		184	189		193		
% Free cholest	32	37	30	30	29	28		27	27	23	—	28	27		28	26		30		
Vit A, megm %	5	5	9	14	24	22		17	26	—	30	24	21		24	—		—		
Carotene, megm %	48	55	76	—	72	96		120	219	195	185	185	200		150	—		—		
Case #44																				
Tot prot, gm %	66	55	63	63		66	6.5		64	64		63	68		68			61		
Albumin, gm %	27	24	28	28		30	3.2		32	36		28	37		42			39		
Globulin, gm %	39	31	35	35		33	3.3		32	28		35	31		26			22		
Tot chol, mg %	145	134	140	—		180	183		173	151		—	149		—			173		
% Free cholest	30	33	29	—		31	30		29	29		—	26		—			29		
Vit A, megm %	19	15	18	—		—	—		—	22		24	—		—			—		
Carotene, megm %	96	86	69	—		—	—		—	104		80	—		—			—		
Case #14																				
Tot prot, gm %	56	—	61	—	61	57	63	—	47	54		56†	64		62	62		63		
Albumin, gm %	24	—	25	—	26	28	27	—	19	20		25	26		26	29		31		
Globulin, gm %	32	—	36	—	35	29	36	—	28	34		31	38		36	33		32		
Tot chol, mg %	169	—	173	—	149	156	146	148	—	143		135	143		110	128		131		
% Free cholest	33	—	31	—	33	33	33	31	—	30		29	30		31	31		27		
Vit A, megm %	12	22	15	26	19	20	12	18	12	19		21	23		11	15		—		
Carotene, megm %	120	180	150	108	114	100	72	100	108	155		150	125		81	75		—		
Case #52																				
Tot prot, gm %	56		57		54		†	65				58	74		75			60		
Albumin, gm %	31		32		27			44				43	47		40			38		
Globulin, gm %	25		25		27			21				15	27		35			22		
Tot chol, mg %	198		178		168			—				190	175		196			232		
% Free cholest	33		33		27			—				33	30		30			31		
Vit A, megm %	—		10		12			—				—	—		—			28		
Carotene, megm %	—		100		45			—				—	—		—			105		

	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
Case #51 (cont.)																		
Tot prot, gm %	6.9			7.5		7.1	—	7.5		6.9		7.4			7.7		7.2	Patient alive and well
Albumin, gm %	3.7			3.5		4.0	—	4.1		3.8		3.8			3.9		3.6	
Globulin, gm %	3.2			3.7		3.4	—	3.4		3.1		3.6			3.8		3.6	
Tot chol, mg %	223					200	—	238		202		207			194		208	
% Free cholest	28			—		27	—	30		26		27			30		28	
Vit A, megn %	—			—		—	—	26		31		—			—		—	
Carotene, megn %	—			—		—	96	106		117		—			—		—	
Case #44 (cont.)																		
Tot prot, gm %	6.7	7.0†				6.8		7.2			7.1		7.1	7.7	7.3		7.0	Patient alive
Albumin, gm %	4.8	4.4				5.0		4.8			5.3		4.5	5.2	4.5		4.9	
Globulin, gm %	1.9	2.6				1.8		2.4			1.8		2.6	2.5	2.8		2.1	
Tot chol, mg %	188	198				164		188		191		205		190	199		221	
% Free cholest	28	33				29		26		27		27		27	27		30	
Vit A, megn %	39	—				—		26		36		40		63	48		—	
Carotene, megn %	51	—				—		135		150		135		166	150		—	
Case #14 (cont.)																		
Tot prot, gm %		5.9				6.4		7.0		6.4		5.8		5.8		6.2	6.1	Patient alive
Albumin, gm %		2.7				3.1		3.3		3.3		3.4		2.9		3.0	2.7	
Globulin, gm %		3.2				3.3		3.7		2.6		2.4		2.9		3.2	3.4	
Tot chol, mg %		120				163		146		171		149		135		158	142	
% Free cholest		20				—		28		29		25		30		29	32	
Vit A, megn %		—				—		17		21		—		—		—	—	
Carotene, megn %		—				—		103		127		—		—		—	—	
Case #52 (cont.)																		
Tot prot, gm %	5.4						6.2†			6.1							6.6	Patient alive and well
Albumin, gm %	2.5						4.0			4.5							4.4	
Globulin, gm %	2.9						2.2			1.6							2.2	
Tot chol, mg %	228						134			178							322	
% Free cholest	26						33			30							26	
Vit A, megn %	30						—			—							117	
Carotene, megn %	150						—			—							150	

* Determinations done on plasma

† Indicates time at which no more paracenteses were required or ascites was controlled

‡ Ascites recurred, associated with hemorrhage, in the 23rd month—controlled, no paracentesis required

22, approximately 94 liters of fluid were removed in 11 paracenteses. The average total protein concentration of the ascitic fluid in this patient was 12 gm %, the average albumin was 0.5 gm %. This meant a loss of 1128 gm of protein from the body economy, about half of which was albumin. The same was true in all of the cases, the total amounts lost depending obviously on the amount of ascitic fluid that accumulated. These data will be reported in greater detail in a subsequent paper.

8 Results of the Thymol Turbidity Determinations The thymol turbidity determinations varied considerably from patient to patient, the range was from 6 to 42 units. No consistent relationship was found to the total serum protein, serum albumin, total cholesterol, or per cent of free cholesterol. There was a quantitative relationship to the total serum globulin and a consistent relationship to the gamma globulin fraction, as is shown in Figure 6. The regression line, calculated by the method of least squares (31), shows that the thymol turbidity units increased in proportion to the concentration of gamma globulin. This is in agreement with the findings of Kunkel and Hoagland (32). It is rather difficult to interpret the thymol turbidity test, in spite of the relationship to the concentration of the gamma globulin. The low levels encountered in many of the patients with advanced cirrhosis, proven in several cases by postmortem examination, make it clear that an increase in thymol turbidity units may not occur in patients with cirrhosis of the liver. This finding is similar to that reported by Kunkel (33).

9 Punch Biopsies and Postmortem Findings Punch biopsies have been done on ten patients and repeated in three during the course of therapy. All of the punch biopsies showed cirrhosis of the liver and in most cases a moderate amount of fatty infiltration. In Cases 4, 17, and 48, punch biopsies were repeated during the course of therapy, and these are shown in Figures 7-9.

Figure 7 (Case 4) shows the punch biopsy taken prior to therapy, at which time the patient had ascites. The section reveals liver tissue of which approximately $\frac{2}{3}$ is replaced by fibrous tissue. There is disorganization of the normal lobular pattern by the fibrous tissue located in the portal regions. Isolated groups of liver cells show fatty change. Proliferating bile ducts are present in the fibrous tissue. The second biopsy (Figure 7) was taken 8 weeks after therapy and shows slight improvement in the microscopic picture. Although fibrous tissue is still present, there is an increase in the amount of intracellular material within the cells. At the time of this punch biopsy the patient had shown clinical improvement, and his previous paracentesis, done 4 weeks prior to the punch biopsy, was the last one that he required. The total serum proteins at this time were 7 gm %, the albumin 3 gm %, and the globulin 4 gm %. The patient was discharged from the hospital 2 weeks after the punch biopsy. By the time of the second punch biopsy he had received 675 cc of liver extract. The microscopic sections show that the process of regeneration of liver tissue in a patient with fibrosis is slow, and yet, as reflected in the serum proteins and in the patient's clinical condition, there was evidence of physiological improvement of liver function.

Case 17, a 42-year-old white male, was admitted to the hospital on October 23, 1947. He was deeply jaundiced, the liver was enlarged down to the costal margin, and he had a severe anemia with a red blood count of 2.5 million and hemoglobin 7.8 gm %. Prior to admission to this hospital he had been treated at another hospital. The first punch biopsy was done on October 30, 1947, before therapy with liver extract was begun. This biopsy (Figure 8) showed a moderately severe degree of proliferating fibrous tissue, disturbing the normal architecture of the liver. Within this fibrous tissue, bile ducts were seen to be pro-

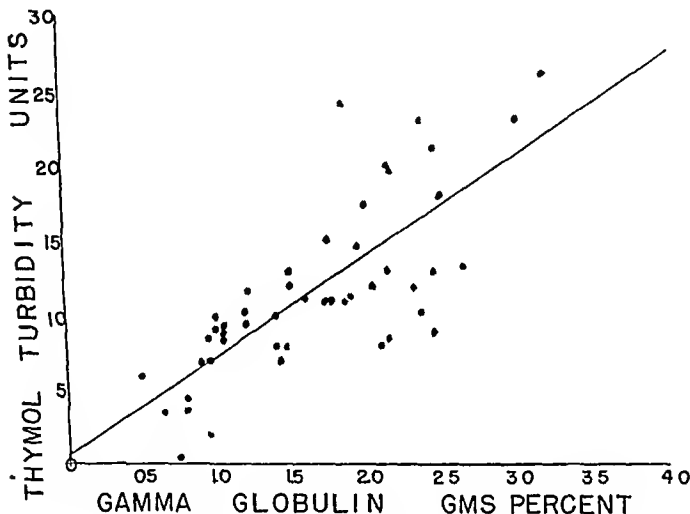


FIG. 6. RELATION OF THE THYMOL TURBIDITY UNITS TO THE CONCENTRATION OF GAMMA GLOBULIN

liferating. Several cells contained fat vacuoles and a few parenchymatous cells had the appearance of regeneration. At the time of this biopsy the total protein was 7 gm %, albumin 3.4 gm %, globulin 3.6 gm %, total cholesterol 321 mg %, free cholesterol 115 mg %, and the per cent free 37, thymol turbidity was 22 units. The second punch biopsy (Figure 8) was done April 27, 1948, after almost 6 months of therapy. The patient had been admitted at this time because of tarry stools. The blood chemistry showed total protein 6.96 gm %, albumin 4.03 gm %, globulin 2.93 gm %, total cholesterol had risen to 500 mg %, with 277 mg of free which meant that 55% of the total was free cholesterol. The red blood count had fallen as a result of bleeding to 2.6 million. The microscopic section revealed marked increase in fibrous tissue, principally in the portal areas dividing the parenchyma into nodules. There is mild fatty change at

TABLE VII

Serum protein, cholesterol, vitamin A*, and carotene* values during course of therapy with intravenous liver extract

	DE- FORE THER- APY	MONTHS OF THERAPY																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Case #51																				
Tot prot, gm %	5.6	5.7†	7.2	6.8	8.1	7.7		7.0	6.7	6.1	—	6.2	6.6		7.0	6.5		7.0		
Albumin, gm %	1.7	1.7	2.5	2.6	3.4	3.4		3.3	3.0	3.2	—	3.4	3.4		3.6	3.4		3.6		
Globulin, gm %	3.9	4.0	4.7	4.2	4.7	4.3		3.7	3.7	2.9	—	2.8	3.2		3.4	3.1		3.4		
Tot chol, mg %	127	111	124	135	138	150		185	175	188	—	188	190		184	189		193		
% Free cholest	32	37	30	30	29	28		27	27	23	—	28	27		28	26		30		
Vit A, megn %	5	5	9	14	24	22		17	26	—	30	24	21		24	—		—		
Carotene, megn %	48	55	76	—	72	96		120	219	195	185	185	200		150	—		—		
Case #44																				
Tot prot, gm %	6.6	5.5	6.3	6.3		6.6	6.5		6.4	6.4		6.3	6.8		6.8			6.1		
Albumin, gm %	2.7	2.4	2.8	2.8		3.0	3.2		3.2	3.6		2.8	3.7		4.2			3.9		
Globulin, gm %	3.9	3.1	3.5	3.5		3.3	3.3		3.2	2.8		3.5	3.1		2.6			2.2		
Tot chol, mg %	145	134	140	—	180	183		173	151			—	149		—			173		
% Free cholest	30	33	29	—	31	30		29	29	22		—	26		—			29		
Vit A, megn %	19	15	18	—	—	—		—	—	22		24	—		—			—		
Carotene, megn %	96	86	69	—	—	—		—	—	104		80	—		—			—		
Case #14																				
Tot prot, gm %	5.6	—	6.1	—	6.1	5.7	6.3	—	4.7	5.4		5.6†	6.4	6.8	6.2	6.2	7.3	6.3	6.1	5.6
Albumin, gm %	2.4	—	2.5	—	2.6	2.8	2.7	—	1.9	2.0		2.5	2.6	3.0	2.6	2.9	3.4	3.1	2.9	2.6
Globulin, gm %	3.2	—	3.6	—	3.5	2.9	3.6	—	2.8	3.4		3.1	3.8	3.8	3.6	3.3	3.9	3.2	3.2	3.0
Tot chol, mg %	169	—	173	—	149	156	146	148	—	143		135	143	146	110	128	141	131	111	150
% Free cholest	33	—	31	—	33	33	33	31	—	30		29	30	30	31	31	31	27	28	27
Vit A, megn %	12	22	15	26	19	20	12	18	12	19		21	23	16	11	15	—	—	—	—
Carotene, megn %	120	180	150	108	114	100	72	100	108	155		150	125	102	84	75	—	—	—	—
Case #52																				
Tot prot, gm %	5.6		5.7		5.4	†		6.5				5.8	7.4		7.5					
Albumin, gm %	3.1		3.2		2.7			4.4				4.3	4.7		4.0					
Globulin, gm %	2.5		2.5		2.7			2.1				1.5	2.7							
Tot chol, mg %	198		178		168			—				190	175							
% Free cholest	33		33		27			—				—	—							
Vit A, megn %	—		10		12			—				—	—							
Carotene, megn %	—		100		45			—				—	—							

Case 17, a 42-year old white male, was admitted to the hospital on October 23, 1947. He was deeply jaundiced, the liver was enlarged down to the costal margin, and he had a severe anemia with a red blood count of 2.5 million and hemoglobin 7.8 gm %. Prior to admission to this hospital he had been treated at another hospital. The first punch biopsy was done on October 30, 1947, before therapy with liver extract was begun. This biopsy (Figure 8) showed a moderately severe degree of proliferating fibrous tissue, disturbing the normal architecture of the liver. Within this fibrous tissue, bile ducts were seen to be pro-

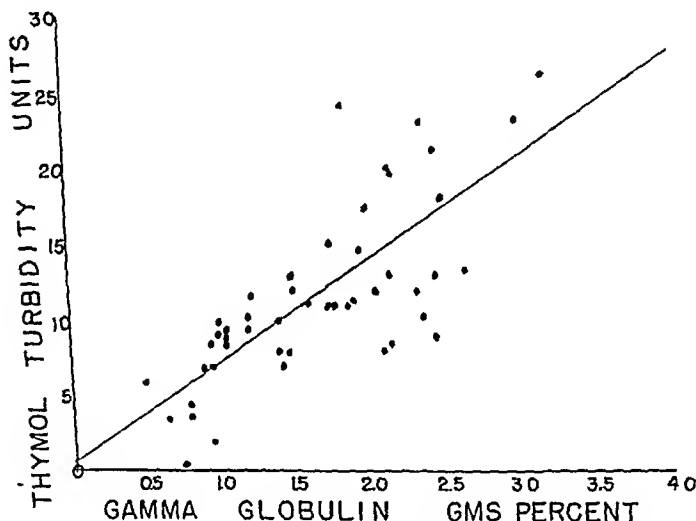


FIG. 6. RELATION OF THE THYMOL TURBIDITY UNITS TO THE CONCENTRATION OF GAMMA GLOBULIN.

liferating. Several cells contained fat vacuoles and a few parenchymatous cells had the appearance of regeneration. At the time of this biopsy the total protein was 7 gm %, albumin 3.4 gm %, globulin 3.6 gm %, total cholesterol 321 mg %, free cholesterol 115 mg %, and the per cent free 37, thymol turbidity was 22 units. The second punch biopsy (Figure 8) was done April 27, 1948, after almost 6 months of therapy. The patient had been admitted at this time because of tarry stools. The blood chemistries showed total protein 6.96 gm %, albumin 4.03 gm %, globulin 2.93 gm %, total cholesterol had risen to 500 mg %, with 277 mg of free which meant that 55% of the total was free cholesterol. The red blood count had fallen as a result of bleeding to 2.6 million. The microscopic section revealed marked increase in fibrous tissue, principally in the portal areas dividing the parenchyma into nodules. There is mild fatty change at

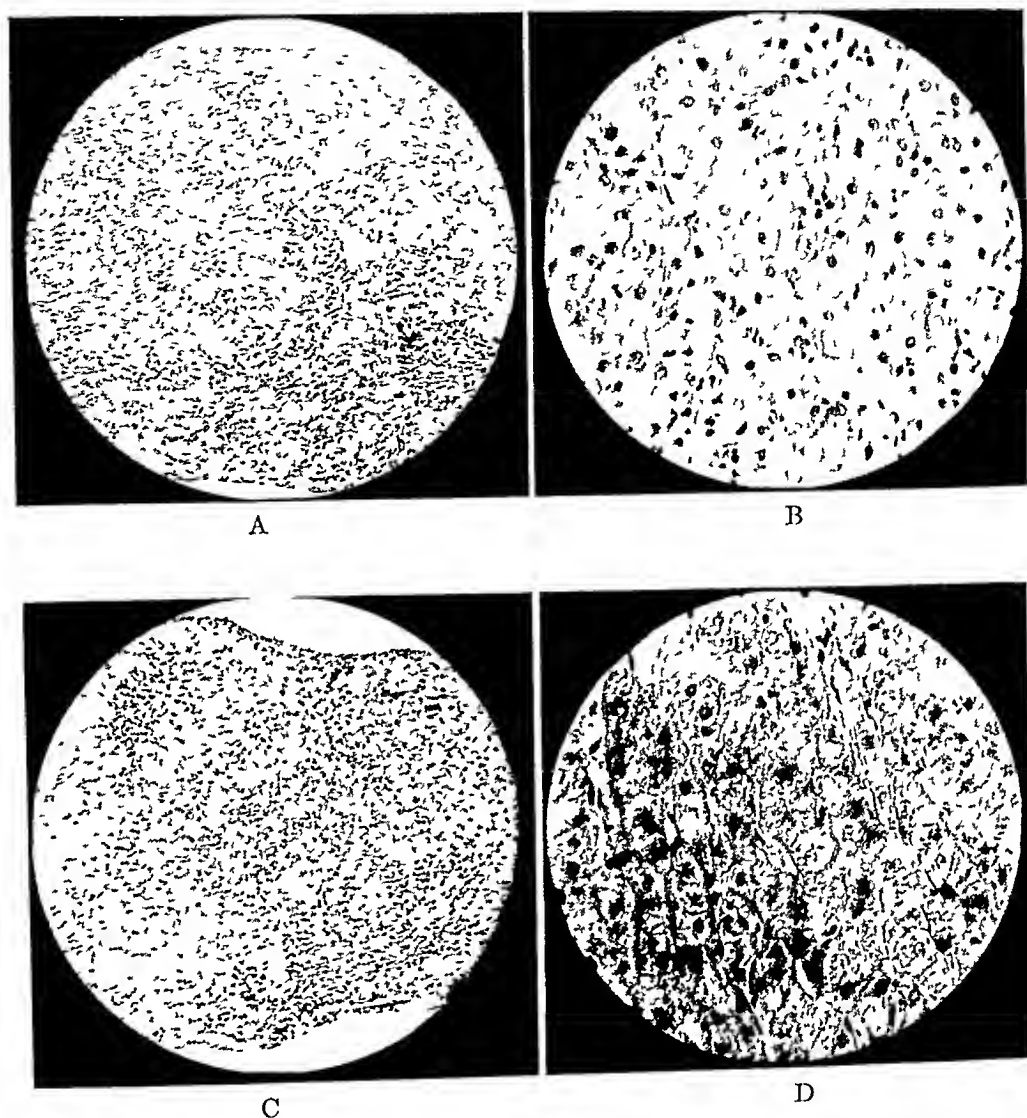


FIG 7

Case 4, First Punch Biopsy

A, left Photomicrograph of a section of a punch biopsy of the liver showing a large area of portal scarring containing numerous small bile ducts and disorganizing the hepatic lobular architecture

B, right Higher magnification of A, showing the disorganization of the hepatic lobular architecture

Case 4, Second Punch Biopsy

C, left Photomicrograph of the second punch biopsy, taken after 6 weeks of therapy, shows portions of several lobules with small periportal scars. The parenchymal cells are prominent, presenting a vacuolated appearance which is probably attributable to the glycogen, as fatty infiltration was minimal

D, right High power of a portion of C, showing leucocytic infiltration in one area. Note the increase in intracellular material, as evidenced by the intensity of the staining reaction

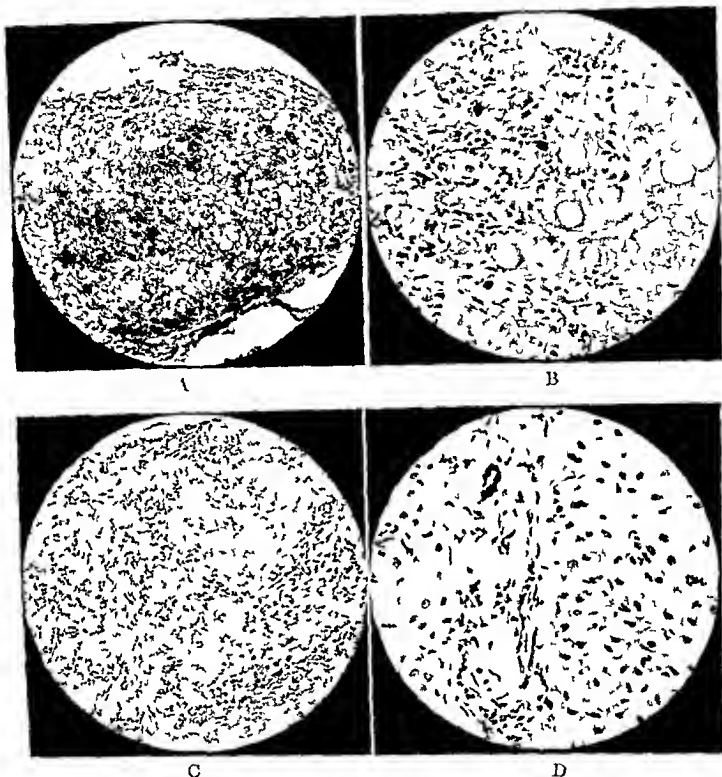


FIG 8

Case 17, First Punch Biopsy

A, left Photomicrograph showing a low power view of the punch biopsy, which contains an island of disorganized liver tissue surrounded by proliferated connective tissue. Note the variable lipid globules and the increased cellularity among the trabeculae.

B, right Higher magnification of a portion of A, showing the variation of parenchymal cell size and preservation. In the upper portion of the field there are several cells which are undergoing degeneration, and among the parenchymal cells there are increased numbers of polynuclear leucocytes (superimposed necrotizing hepatitis). This is the type of lesion from which regeneration is unlikely, owing to the widespread destruction of parenchymal cells.

Case 17, Second Punch Biopsy

C Low power photomicrograph of the second punch biopsy, 6 months after the first, showing the scarring noted previously, disorganization in the hepatic parenchyma, but less lipid in the recognizable parenchyma.

D, right Higher magnification of a field in C, showing the parenchymal cells near a portal scar, with less lipid than that seen in the cells in the first biopsy. Note in the upper portion of the field 2 cells with double nuclei, suggesting that regeneration has occurred.

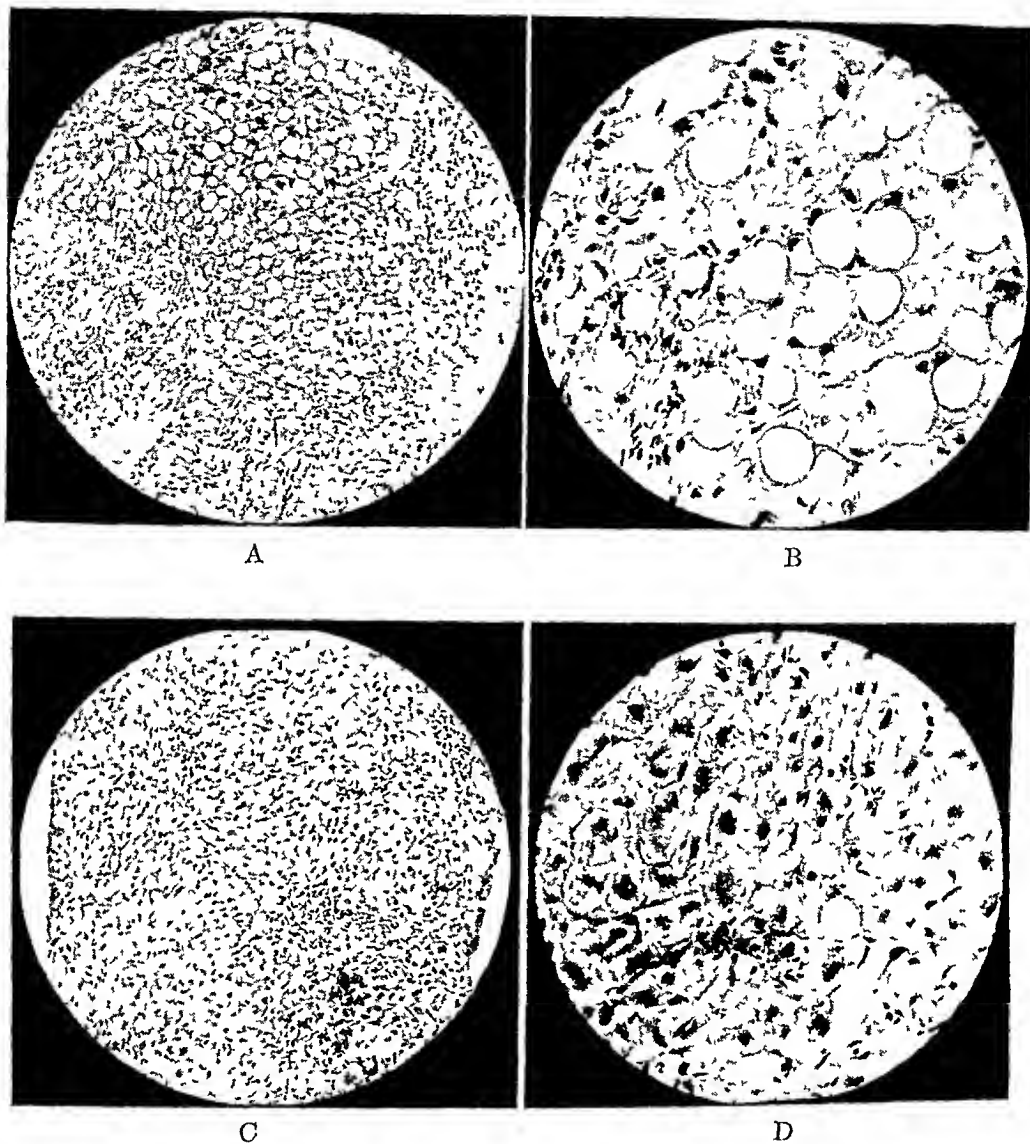


FIG 9

Case 48, First Punch Biopsy

A, left Low-power photomicrograph showing an island of liver parenchyma surrounded by scar tissue in the adjacent portal canal. Note the large amount and variation in the size of the lipid globules.

B, right Higher magnification of a field in the parenchyma of A, showing the lipid deposition and the slight polynuclear leucocytic infiltration around some of the degenerating liver cells.

Case 48, Second Punch Biopsy

C, left Second punch biopsy, low power, shows a mild portal fibrosis, a reduction in lipid content in the liver parenchyma, with an increase in solid cytoplasm.

D, right Higher magnification of a field in C showing the return of the liver cell nuclei to the center of the cells after lipid material has receded. There is still some bile pigment in some of the cell, but no leucocytic reaction. There is a single focus of cellular infiltrate which is an extension from a portal scar.

places Proliferating bile ducts are seen in the fibrous tissue There is infiltration of mononuclears and lymphocytes as well

Case 48 was admitted to the hospital March 24, 1948 He was a 42-year-old white male, deeply jaundiced The liver was greatly enlarged down to the umbilicus The first punch biopsy (Figure 9) was done March 30, 1948 At this time the total protein was 8.2 gm %, albumin 2.8 gm %, globulin 4.5 gm %, total cholesterol 288 mg %, free cholesterol 100 mg %, and the per cent free 35% The red blood cells were 3.9 million The first punch biopsy showed moderate increase in fibrous tissue, principally in the portal areas but also to some extent in the lobules This fibrous tissue contains a small number of proliferating bile ducts but also is infiltrated with a small number of lymphocytes, mononuclears and scattered polymorphonuclear cells The parenchymal cells have undergone marked fatty change A large amount of bile is present within the parenchymal cells The second punch biopsy (Figure 9) was done May 27, after approximately 6 weeks of therapy The patient had improved clinically and was discharged from the hospital 2 weeks later At the time of this biopsy the total protein was 7.4 gm %, albumin 3.4 gm %, globulin 4.0 gm % Total cholesterol, done 3 weeks later, was 203 mg %, and the per cent of free cholesterol had dropped to 25 The punch biopsy showed a moderate increase in the fibrous tissue of the portal areas Compared to the previous biopsy there is a milder degree of fatty change and somewhat less bile pigment It was not possible in this small specimen to determine whether there was an appreciable alteration in the degree of cellular infiltration Postmortem examinations were done on twenty of the patients in Group I and on fourteen of the patients treated with liver extract intravenously

DISCUSSION

Any method of therapy in the treatment of a disease with as widespread effects as cirrhosis of the liver is tedious, time consuming, and very often discouraging This, added to the fact that the fibrosis resulting from the liver injury probably is a permanent effect, makes it obvious that although the patients may improve clinically and objectively, with respect to the serum proteins and cholesterol fractions, they can never be considered as "cured" The purposes of the treatment are to improve the functional capacity of the liver by stimulating regeneration of parenchymal cells, to restore the blood constituents to a normal pattern, and to improve the nutritional state of the patient The liver has an unusual capacity for regeneration, the extent of which depends to a considerable degree on the maintenance of circulation through the liver (13, 14, 36) According to Stephenson (14) in experiments on rats, the amount of restoration of liver tissue appeared to be directly proportional to the amount of restriction of the portal vein, which in his experiments was effected by partial ligation of the portal vein In view of these findings it is reasonable to infer that the pathological changes present in the "cirrhotic" liver would handicap regeneration or restoration of the liver Mann and his collaborators (37) showed experimentally that restoration of the liver after partial removal was almost absent in dogs in whom cirrhosis had been pro-

duced by carbon tetrachloride. Mann, who also points out (13) the importance of the portal circulation for restoration of the liver after partial removal, reported that regeneration of hepatic tissue after injury appears to begin in the islands of seemingly normal hepatic cells that are supplied mainly or entirely by arterial blood, while the cells in the regions supplied only by the portal blood may be too badly injured to regenerate. These observations fit in with those reported by Himswoth (38) which led him to define two principal types of hepatic damage. The first, referred to as "zonal" necrosis, is characterized by damage to a particular region within the liver lobule, and, although considerable amounts of parenchymal tissue may be destroyed, the rim of parenchymal cells surviving in each lobule provides a source from which new parenchymal cells can regenerate. Himswoth refers to the other type of necrosis as "massive." This, which involves the whole lobule, is the acute yellow atrophy of older writers, and as no rim of parenchymal tissue survives, regeneration cannot take place in the affected areas. Necrosis of the liver is followed by fibrosis, of which there seem to be two distinct types. Post-necrotic scarring, which usually follows the massive type of necrosis, leaves an organ cut into by coarse bands of fibrous tissue with separate areas composed of normal liver lobules. The other is the diffuse fibrosis and commences as a thickening of the reticulin fibers in the region of the portal tract or central veins and involves every lobule. It is clear that the anatomical form of the original hepatic lesion has a bearing on the consequences of hepatic injury, and it would seem also to have an important influence on survival in patients with liver disease. The type of damage resulting from massive necrosis is usually associated with jaundice and evidences of severe toxemia, and if sufficiently widespread, would interfere with regeneration of enough liver cells to permit restoration of function. On the other hand, in the diffuse hepatic fibrosis, which is the lesion typical of the classical picture of portal cirrhosis, regeneration of liver parenchyma is possible if the fibrosis has not advanced too far. The fact that the patients receiving liver extract intravenously survived longer and were in a better state of nutrition than the patients in the control group suggests that the growth-promoting factors in the liver extract may have been a factor in stimulating regeneration of liver cells. Although the data on the patients receiving the larger doses of liver extract is still limited, their response to therapy adds support to the suggestion that some substance or substances in the extract are influencing restoration of the liver. Patek's group (30), in whom the survival is better than that reported by other investigators, received dried brewers yeast, which also contains growth-promoting factors (25, 26). In the patients reported by Labby et al. (8), liver extract in doses ranging from 20 to 60 cc weekly was given. Survival data in this group has not been calculated by the method reported for our and Patek's series (30) and the period of observation only averaged 24 months. However, these authors report (8) that ascites disappeared in twelve of twenty-one patients and that 77 per cent of the group survived 2 years. If the suggestion is correct that growth factors are important in stimulating regeneration of the parenchymal liver cells, it is important to determine whether

there is a single effective factor or whether a combination of factors is responsible for the effect

Our original observation (39) that the reaccumulation of ascitic fluid may precede any significant increase in the albumin level of the serum is borne out by the studies in these cases. That the level of serum albumin is not the sole determining factor in the control of ascites is illustrated in the cases reported in Table VII in whom ascites was controlled in spite of a persistently low albumin level. In most of the cases, once reaccumulation of ascitic fluid was controlled, the serum albumin increased. This sequence of events (i.e., cessation of ascitic fluid reaccumulation preceding a rising serum albumin) is not unreasonable, as once protein is not diverted into the ascitic fluid, the concentration in the serum, and probably also in the tissue cells, may increase.

The patients receiving the liver extract intravenously withstood an unusually large number of paracenteses and, as a result, the removal of unusually large amounts of ascitic fluid. There have been occasional cases reported in the literature where an unusual number of paracenteses have been done during the course of cirrhosis of the liver, but there is some question as to the accuracy of diagnosis (40, 41). The development of ascites has been regarded as a serious prognostic sign, and Ratnoff and Patek (42) showed that after the onset of ascites in a group of 296 patients, 32% survived for one year and 17% survived for 2 years. In only an occasional report is there accurate data on the absolute amounts of ascitic fluid removed during the period of survival. The data that we have presented in the intensively treated group (Group II) is interesting both because of the large amounts of ascitic fluid removed and because it represents the loss of large amounts of protein from the body economy, and indicates that in spite of the liver damage, albumin is being formed.

Regardless of any method of therapy, the outcome in patients with cirrhosis of the liver may be terminated abruptly by hemorrhage from varices. This occurred in both groups reported. Although it is admittedly difficult to evaluate the effect of a single therapeutic agent in a disease as widespread and as damaging to the body as cirrhosis of the liver, in these two groups the therapy was similar except for the fact that Group II received large doses of liver extract intravenously. The extent of liver damage, as judged by determination of serum proteins and cholesterol and its fractions, was similar in both groups. Clinically the patients were about equally ill and as may be determined from the tables, the average duration of the disease prior to treatment was approximately the same. However, survival in the group treated with liver extract intravenously was significantly more prolonged than in the patients treated in the conventional manner.

SUMMARY

The course of cirrhosis of the liver has been observed in a group of 112 patients. 44 of these patients were treated in the conventional manner, i.e., a nutritious diet, large doses of vitamin B complex, and in many cases liver extract intramus-

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ROCKY MOUNTAIN SPOTTED FEVER¹

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CONTENTS

Introduction	333
Relation to other rickettsial diseases	334
History	334
Epidemiology	335
Organism	335
Vector	335
Mammalian reservoir	337
Distribution of cases	337
Prevention	340
Personal measures	340
Vaccination and other specific measures	340
Community measures	342
Natural History of the Disease in Human Beings	342
Exposure	342
Symptoms	342
Rash	343
Other physical findings	343
Course	344
Pathologic anatomy	345
Pathologic physiology	347
Differential Diagnosis	350
Prodromal symptoms	350
Rash	350
Laboratory Tests	351
For diagnosis	351
For control of therapy	353
For prognosis	356
Treatment	357
Specific	357
Supportive	362
Complications	365
Circulatory disturbances	365
Pneumonia	366
Necrosis	366
Prognosis and Mortality	367
In untreated cases	367
In treated cases	367
In reinfections	368

INTRODUCTION

Rocky Mountain spotted fever, one of the rickettsial diseases, is a generalized infection of unusual severity, which occurs when a human being is accidentally bitten by an infected tick. Man is only incidentally involved, since the disease

¹This study was aided by a grant from the John and Mary R. Markle Foundation

is primarily an infection of ticks and secondarily one of small animals. In all the rickettsioses, the arthropod is little affected by the infestation, in Rocky Mountain spotted fever it serves as a reservoir in nature as well as the vector.

The tolerance of arthropods for rickettsias suggests a very long standing association which might even be called a symbiosis (1). In epidemic typhus the human body louse serves as the vector to transmit the disease from man to man. In endemic typhus the rat flea serves as the vector, transmitting the disease from rat to rat and from rat to man. In scrub typhus the mite is the vector, the wild rat and possibly other wild rodents are apparently the natural reservoirs. Q(ueensland) fever is a natural infection of wild animals transmitted in nature by ticks, which can also transmit the disease to domestic cattle; it is not known exactly how man is infected from animals. Rickettsialpox is transmitted by a rodent mite from house mice to man (2).

Rickettsial diseases of man which are related to spotted fever and transmitted by ticks are of world-wide distribution. Rocky Mountain spotted fever of North America is apparently identical with the disease in South America, where it has been called São Paulo typhus. In Mediterranean countries *fièvre boutonneuse*, which is also called Marseille fever and *escarbo-nodulaire*, differs only in the fact that the primary site of inoculation is evidenced by an ulcer. In Africa, Kenya fever and South African tick-bite fever are apparently related to Rocky Mountain spotted fever. In other parts of the world—North Queensland, India, and Russia—tick borne rickettsioses are often called tick-typhus. All of these strains of rickettsias appear to be immunologically related (3).

Rocky Mountain spotted fever was first recognized in the valleys of the Northern Mountain states. The disease was apparently first recorded in 1896 by Major W. W. Wood, who collected descriptions of cases from eight Idaho physicians and transmitted his report to the Surgeon General of the Army (4). The cases occurred in the neighborhood of Boise and in the Snake River Basin, they were mild and the mortality was low. Maxey of Idaho, in 1899, published the first clinical account and gave a vivid description of the symptoms and signs. In 1902 McCullough of Montana described the virulent form with high mortality, which had been recognized for many years in the Bitter Root Valley. Later in the same year, Wilson and Chowning reported their investigations of the disease in Montana and suggested that it was transmitted by the bite of the wood tick (5). The proof that the disease was transmitted by ticks was offered in 1906 by Ricketts and independently by King, in the following year, Ricketts demonstrated the occurrence of naturally infected wood ticks in the Bitter Root Valley (6, 7). Ricketts had previously shown that the disease could be experimentally transmitted to guinea pigs and monkeys by inoculating them with blood from naturally infected human beings (8).

Ricketts and his associates made fundamental contributions to our knowledge of the organism, the vector, the mode of infection, and the immunology of the disease, and sketched in broad outline the mode of attack on the problem. Wolbach in 1919 published his classic studies on the etiologic agent and the pathology of the disease in ticks and human beings (4). His careful and exhaustive micro-

scopic studies demonstrated, among other findings, the intranuclear multiplication of the rickettsias in tick tissue. The understanding of the abnormal physiologic changes in man resulting from the infection and the design of a rational approach to therapy are based on Wolbach's research.

EPIDEMIOLOGY

Organism

The rickettsia of spotted fever, like all rickettsias, is a tiny micro-organism which is found intracellularly but which requires special staining methods for its demonstration. Wolbach named the organism *Dermacentrozetes rickettsi*, and most authors follow this nomenclature. Bengston in Bergey's "Manual of Determinative Bacteriology" calls it "*Rickettsia rickettsi* (Wolbach)" (9). Pinkerton has discussed the classification and the nomenclature of all the rickettsias and summarizes the viewpoints of Philip and others (2, 10).

In smears of mammalian tissues the organisms are pleomorphic and may appear as minute paired organisms, lanceolate in shape, surrounded by a narrow clear zone or halo and resembling a pair of pneumococci, or they may be seen as slender rod shaped forms sometimes exhibiting polar granules. The Giemsa, Macchiavollo and Castaneda stains each bring out different characteristics. Like other rickettsias, the organisms stain poorly by the usual techniques and appear gram-negative. The number of rickettsias found within cells is smaller in mammals infected with spotted fever than in those infected with typhus. The organisms are found predominantly within the nuclei of cells, a very unusual location for micro organisms, they are also found in the cytoplasm in small numbers (1, 2, 3, 4).

In the tick there are bacillary, curved and club-shaped forms, smaller rods with deeply staining chromatoid granules, and more deeply staining lanceolate forms. A very minute form may appear in tightly packed masses in the nuclei of certain cells.

The organism will grow and reproduce only in the presence of living cells. In tissue cultures of mammalian cells grown in plasma the optimum temperature for growth is 32°C, in fertile hens' eggs the optimal temperature for growth is 35°C. The organisms will remain viable for a short time in ordinary bacteriologic culture media, in blood, or in infected tissue kept at room temperature without special means of preservation. They may be preserved in the frozen state for months. The organisms are readily inactivated by moist heat and are destroyed by a temperature of 50°C in ten minutes. A wide variety of chemical disinfectants readily kill the rickettsias. The organisms are susceptible to drying and are destroyed by desiccation in 10 hours. The spotted fever strain of rickettsias does not pass the usual Berkefeld filter candles or Seitz filter pads.

Vector

This rickettsial disease is primarily an infestation of ticks. The organism induces no cellular reaction in the tick, and apparently does it no harm. The

rickettsias are passed to the eggs of the adult female by copulation with an infected male, or by infection from the maternal generative organs during cell division and formation of the egg. Thus the vector may be infected at all stages—a distinctive feature of the spotted fever strain of rickettsias. The life cycle of the tick is very complicated, and the rickettsias show a cyclic morphology in the various stages, the nuclei of cells of almost all tissues are invaded in all stages of the life cycle. While a large variety of ticks are experimentally capable of transmitting the disease in the laboratory, only ticks found infected in nature are epidemiologically important. The wide geographic dispersal of the proved and potential vectors is discussed by Cox (3).

The association of the wood tick, *Dermacentor andersoni*, with the transmission of the disease was recognized in 1902 by Wilson and Chowning (5). This tick is found throughout the Rocky Mountain region and adjacent areas. *Dermacentor variabilis*, the American dog tick, is found in the Great Plains region and eastward to the Atlantic coast; to the south it reaches into Mexico, in Canada it occurs eastward from southern Manitoba to Labrador (11). These two species of ticks are the chief vectors for transmission of the disease to man, their life cycles may cover two years.

The larval form may be congenitally infected by transovarian transmission. Since it feeds on a great variety of rodents and certain small carnivores, some of which are susceptible to spotted fever, it may also acquire the infection in this manner. Few larvae survive the complicated life cycle, however. The nymphal form hibernates through the winter. It feeds on many varieties of rodents, including rabbits. Nymphs occasionally have been found attached to children. The adult tick bites man readily, although it mainly infests large wild and domestic animals; *D. variabilis* occurs in abundance on dogs, for instance. The adult ticks hibernate through the winter.

The percentage of infected ticks in an endemic area is not great; it varies from year to year in each area, but is usually in the range of 3 per cent (7).

The wood tick becomes active during the spring and early summer as the snows melt, but may retreat to shady areas and become less active in hot midsummer. The dog tick appears in late spring and remains active longer during the summer. In the South occasional ticks have been found active during the winter.

Ticks live on moist ground covered with small bushes and shrubs, where numerous small and large mammals serve as hosts and as a source of blood for food. They hang from the lower branches of the vegetation, waving their legs, and transfer with great rapidity to the hair of passing warm-blooded animals. The presence of blood in the intestinal tract of the tick for two to eight hours apparently stimulates the virus in some fashion, so that its virulence and infectivity are increased. The period of attachment required for activation of the rickettsias is greater in the early spring than in midsummer, when the organisms have reached maximum virulence for the season.

The rabbit tick, *Haemaphysalis leporis-palustris*, does not attack man, but is important in the epidemiology of the disease because it feeds on rabbits (12).

Rabbits infected by this tick may transmit the rickettsias to the immature forms of *D. andersoni* and *D. variabilis* which feed simultaneously on the rabbit host. The rabbit tick completes its life cycle in one year, and consistently carries an extremely mild strain of spotted fever rickettsias. It is prevalent in the northern United States and is active from early spring to early fall, but in the South the period of activity is considerably extended.

Mammalian reservoir

In spite of the extensive research done on rickettsial spotted fever over many years, no naturally infected animal has been found in the United States. Jellison has pointed out the close geographic relationship which exists between cases of spotted fever in human beings and one species of cottontail rabbit, *Sylvilagus nuttalli*, this evidence is circumstantial and was accumulated only for twelve states in the northwestern United States (13). Many mammals can be experimentally infected with spotted fever rickettsias. When the disease is experimentally transmitted to young dogs and certain other mammals, the infection may be very mild, with no visible diagnostic lesions or distinctive febrile reaction, immunologic tests, however, will demonstrate the development of a positive Weil-Felix reaction, or of complement-fixing or other antibodies.

In Brazil the opossum, rabbit, guinea pig, and domestic dog have been found naturally infected. In the Mediterranean area the evidence indicates that dogs are probably the chief animal reservoir. Naturally infected dog ticks have been removed from dogs in the houses of patients with Kenya fever (3).

Clinically and pathologically, the disease in animals duplicates that in man to a greater degree than any other infectious process, this statement is true irrespective of the manner of infection—tick bite, feeding of infected material, or subcutaneous or intraperitoneal inoculation with infected blood. The pathologic studies in animals indicate that the disease distinctively involves the blood vessels, chiefly of the skin and central nervous system (4).

Distribution of cases

Rocky Mountain spotted fever occurs in endemic form throughout most of the United States. For many years it was regarded chiefly as a disease of the Rocky Mountain and Pacific states, although occasional cases were reported in the North Central area. The disease was identified in the East in 1931 (14). As is often true, recognition of the disease has led to more accurate reporting of cases. It is not likely that spotted fever has recently spread from the West to the Eastern and Central states, it has probably been endemic in these areas for many years. The disease has not been reported from Vermont. To judge by the number of cases reported during the period of 1939 to 1947, spotted fever must be quite rare in Arizona, Florida, Maine, Michigan, Minnesota, Nebraska, New Hampshire, Rhode Island, and Wisconsin. Some cases reported from these states are known to have been contracted elsewhere.

The total number of cases reported in the United States as a whole has remained reasonably constant, during the period from 1939 to 1947, it averaged

around 500 cases yearly (table 1). The two important endemic foci at present are the Rocky Mountain area—Wyoming, Montana, and Colorado—and the South Atlantic states—Virginia, Maryland, and North Carolina. The number of cases reported in the West, especially in Montana and Wyoming, began to decline around 1944, probably as a result of the application of effective preventive measures, the number of deaths has not declined in the same proportion as the number of cases. The mortality remains fairly high throughout the United States, averaging 23 per cent in 4033 cases reported during the period from 1939 to 1946 (table 2)

The severity of the infection in any given area remains fairly constant, even though it may vary widely in adjacent areas of essentially similar geographic characteristics. For instance, the mortality in unvaccinated adults in the Bitter Root Valley of Montana has been for years more than 80 per cent; when the disease was more prevalent in southern Idaho, the mortality was less than 5 per

TABLE 1
Cases 1939-1947

	1939	1940	1940	1942	1943	1944	1945	1946	1947
West									
Wyoming	47	61	82	38	32	30	14	13	9
Montana	32	32	107	45	28	5	2	9	6
Colorado	16	10	21	16	12	8	13	10	11
East									
Virginia	50	46	33	47	56	81	99	92	67
Maryland	72	55	45	59	58	64	47	58	66
North Carolina	41	32	20	35	36	59	57	66	88
United States total	560	457	516	499	467	470	475	589	553

The cases reported annually to the United States Public Health Service from three states in the East and in the West where Rocky Mountain Spotted Fever is most prevalent are recorded for comparison with the figures from the United States as a whole

cent. This variation reflects the inherent difference in the virulence of local strains. There are, however, in any given area, fluctuations in the number of cases and in the mortality from year to year. These are influenced more by the weather—and hence the appearance and activity of ticks—than by variations in the organisms or the possible reservoirs. The fluctuations in severity from year to year are illustrated by the figures from North Carolina, where one of the more virulent strains is found. Between 1938 and 1947, in roughly comparable numbers of cases, the mortality has varied from 19 to 36 per cent. The death rate in the areas where the disease is most prevalent in the West and East, as compared with the United States as a whole, is given in table 2.

Throughout the United States more cases occur during the month of July than in any other, cases are fewest from December through February. In the West the majority of the cases appear between April and June, in the East the

disease is most prevalent during July and August with moderate numbers of cases reported in June and September. Scattered cases may occur earlier or later, depending upon the severity of the winter and whether the seasons are early or late.

The age distribution of the cases in the various areas reflects the occupational activity of the population and the proximity of the vector to human habitations. Few cases are contracted in the city. In the sagebrush and desert regions of the western United States, most infections occur in men who work there the year around—sheepherders, hunters, trappers, prospectors, miners, surveyors, highway and railroad maintenance workers, and forest service personnel. Occasional

TABLE 2
Mortality 1938-1948

	CASES	DEATHS	MORTALITY
			%
West			
Wyoming	317	58	18.3
Montana	260	63	24.2
Colorado	106	26	24.5
West total	683	147	21.5
East			
Virginia	504	92	18.3
Maryland	458	86	18.8
North Carolina	346	96	27.7
East total	1308	274	20.9
United States total	4033	929	23.0

The United States Public Health Service reports for the three states in the East and in the West where Rocky Mountain spotted fever is most prevalent have been summarized for comparison with the figures for United States as a whole.

visitors, such as fishermen, campers, tourists, and picnickers, will sometimes contract the disease.

In the East, since the vector is the common dog tick which infests household pets, the disease is predominantly one of children, and is contracted in suburban or rural areas. Many cases occur in vacationists or people seeking recreation. Of 474 cases reported in North Carolina during the period from 1938 to 1947, 215 were in children under 10 years of age, 113 in the 10-19 year age group, 28 in adults 20 to 29 years old, 59 in the group from 30 to 44 years, and 59 in persons over the age of 45. In children, the incidence of cases was higher in females; in adults, the incidence was greater in males. Taking all ages into consideration, however, the cases were distributed rather evenly between the sexes.

PREVENTION

Personal measures

Control of the infection in nature is not feasible. The greatest protection to an individual lies in preventing the attachment of a tick to the skin or in removing it before the rickettsias have become "activated." Ticks usually transfer from vegetation to the clothing at a height of 18 inches or less from the ground; they will then crawl up the clothing and, at the first opening, approach the skin. High boots, leggings, puttees, or socks worn outside the trousers will hinder the tick from attaching itself to the leg or crawling up it. If there are no openings in the clothing at the ankle, belt line, or shirt front, the tick will continue, over the space of several hours, to crawl up the clothing, attaching itself at a favorite spot on the neck. It is wise, therefore, in tick infested country to pass the hand frequently over the back of the neck and behind the ears. Any tick observed on the clothing should be removed at once before it has a chance to reach the body (12).

Once on the skin ticks seldom attach themselves immediately, after becoming attached, they rarely transfer the infection until they have fed for several hours. It is usually sufficient, therefore, to inspect the body and clothing twice daily when in tick infested country. All clothing should be removed in the search for ticks, clothing should not be laid on the ground, since ticks may crawl onto it. Ticks transfer from dogs to children with ease. The children should be stripped before the midday nap and when coming in from play for the evening meal, a thorough inspection of the skin and hair should be made.

If a tick is found attached to the skin, it should be removed immediately and as gently as possible so as not to squeeze feces out of the insect. It is desirable to detach the tick by slipping small forceps or a hypodermic needle under the mouth parts and lifting it off. If the tick is pulled off with the fingers, it would be advisable to handle it with a small piece of paper. The small wound caused when the mouth parts and the tiny piece of attached skin come out with the insect should not be traumatized by scratching or squeezing, since tick feces may be accidentally inoculated into the raw area. The abrasion should be touched with any available disinfectant, such as iodine or a mercurial antiseptic, or simply be washed with soap and water.

Attempts are being made to develop a tick repellent which can be placed on the body or impregnated in the clothing, no completely satisfactory agent has yet been found, although some give promise (15). The ordinary mosquito repellents are ineffective. No material is known which can be fed to dogs or other animals to repel ticks or to prevent them from becoming attached.

Vaccination and other specific measures

Vaccines which have definite protective value are available. The degree and duration of protection vary with the immune response of the individual vaccinated; the period of effective immunity is less than a year, however. Even more important factors in determining infection of an individual are the virulence of

the infecting strain of rickettsia and the size of the inoculum transferred from the tick. The original vaccine was prepared at the Rocky Mountain Laboratory of the National Institute of Health from the tissues of infected wood ticks (12). This vaccine gives effective protection, but also produces many local and occasional severe systemic reactions. A more satisfactory vaccine has been prepared from rickettsias grown in the yolk sacs of fertile hens' eggs. The reactions to this type of vaccine are much less frequent and severe than with that prepared from ticks. The immunizing power of the two types of vaccine is comparable.

Either vaccine should be injected subcutaneously or intramuscularly in three doses of 1 cc each, or two doses of 2 cc each, given five to seven days apart. In allergic individuals, it is wise to give an intradermal skin test before administering the first dose of vaccine. A full course of vaccine should be given each season in the late winter and early spring, approximately one month before ticks are expected to appear. It is doubtful that immunization after a tick bite has occurred is of any value.

In the West, individuals who are living in highly endemic areas or in localities where the strain is of great virulence, and individuals whose occupation takes them into such areas should be regularly vaccinated. Tourists or vacationists should be vaccinated if their trip to endemic areas will expose them to ticks. In the East, it is doubtful that all children should be immunized. Children in counties where the disease is most prevalent (these counties can be determined by spot maps obtained from the various state health departments) might well be immunized yearly until the age of 15. The administration of the vaccine to adults who hunt or fish frequently or who take regular camping and hiking trips in the country is worth while.

The effectiveness of the vaccine has been demonstrated by Parker (12). Over a period of several years in western Montana there were 38 deaths in 50 non-vaccinated adults (a case fatality rate of 76 per cent), and only three deaths in 59 persons who had been vaccinated within the same year (a mortality of 9 per cent). It can be seen that the immunization did not prevent clinical infection in some people, but that the disease was much less severe in vaccinated individuals. Protection is usually adequate to prevent clinical disease resulting from infections with the relatively mild strains of spotted fever, against the highly fatal type, children are more fully protected than adults. However, previous immunization may mean the difference between life and death if an infection is acquired.

Whether immune antiserum would be of value prophylactically after exposure is unknown. Chemotherapy administered prophylactically or after exposure has not yet been shown to be effective. It is not likely that para-aminobenzoic acid (PABA) would be effective in completely preventing the disease. Aureomycin or Chloromycetin, two antibiotics which are discussed in more detail below, may be found to have suppressive properties. Since no method is available for differentiating between infected and non-infected ticks, the drugs would have to be taken regularly while the individual was in an endemic area. This procedure is impractical for persons living in such a locality, but might be used for periods of a few days by vacationists. Unless administration of the drugs is continued for 3 weeks

after the exposure is terminated, withdrawal may be followed by a delayed atypical form of the disease.

Community measures

The clearing of brush, weeds, and other vegetation around houses or cabins has some limited value, since it removes from the immediate vicinity shelter for the vector and animal reservoir. Spraying an area with DDT or other insecticides is impractical because of the huge territory which would have to be covered and the difficulty in getting under low vegetation. Furthermore, the procedure has not yet been proved to be completely effective (11).

NATURAL HISTORY OF THE DISEASE IN HUMAN BEINGS

Exposure

A history of a trip into a known endemic area, of exposure to ticks in the woods, fields, and ranges, or of exposure in the handling of dogs or sheep may be obtained. It may be important to know how the tick was removed, whether it was crawling or attached, and whether it contained blood. Children, of course, may not notice the tick, or, while they are ill they may not recall having been bitten. The bite is painless and no local lesion is produced.

Rickettsias may remain alive in fresh or dried tick feces for a matter of hours. It is possible that rickettsias contained in feces deposited by ticks on dogs or sheep may enter the circulation of the human victim through scratches or other minor abrasions. This means of infection may account for the failure to obtain a definite history of an attached tick in a moderately high percentage of cases. Infection in laboratory workers is not rare. However, cross infection from one individual to another through the medium of blood or excreta is practically unknown.

Symptoms

The symptoms described below are characteristic of the disease as it occurs in unvaccinated patients treated only with supportive therapy. In cases where an attached tick containing blood was found, the incubation period has varied from two to 14 days, it tends to be shorter—five days or less—in the more severe infections, and longer in the milder ones. In areas where ticks are prevalent, the great number of the insects and the frequency with which they are found on the person make it difficult, if not impossible, to determine the exact time of infection.

The prodromal period may extend over two or three days, and the gradual appearance of symptoms may make it difficult to establish exactly the date of onset. Among the symptoms which may be noted during this period are headache, malaise, loss of appetite, photophobia, chilly sensations, low fever, and pain in the muscles and joints. On the other hand, the onset may be precipitous, characterized by a distinct shaking chill, severe headache, marked lumbar backache, abdominal pain, vomiting, sweating, and even diarrhea. It is usually impossible to make a diagnosis on the basis of symptoms alone.

As the disease progresses, mental clouding and generalized tenderness become more pronounced, obscuring most other symptoms.

Rash

The appearance of the rash is the earliest dependable diagnostic sign. It may appear on the day following the onset of symptoms, but usually is delayed three to four days. Because the onset of symptoms is frequently indefinite, it is more accurate to date the course of the disease from the day the rash appears. The rash usually is noted first on the ankles and feet, spreading within a matter of hours to the wrists and hands and then gradually toward the trunk and head.

When it first appears, the rash is macular, red, and flat, it blanches with pressure, and may resemble measles. It is more easily seen when the temperature is elevated. Within hours it becomes papular, darker red, and slightly dusky in hue. It becomes fully developed within two to three days, assuming a definitely petechial or purpuric character. Fading on pressure no longer occurs. The hemorrhagic character of the rash can be accentuated, or brought out before it spontaneously appears, by applying a tourniquet or a blood pressure cuff, inflated to a level between the systolic and diastolic pressures, for three to five minutes (Rumpel-Leede phenomenon).

The rash is the visible evidence of the specific lesions which occur in small blood vessels. In mild cases it may be fleeting, and seen only on careful inspection. In severe cases the entire body is covered, including the palms and soles, and the rash may involve the mucous membranes of the palate, pharynx, and cheeks, in fatal cases it frequently coalesces. In severe cases, areas of necrosis or gangrene may appear in the rash as the disease progresses.

During convalescence the rash turns brown, and branlike desquamation may occur. Scarring is infrequent unless necrosis or gangrene was present.

Other physical findings

Once fever has appeared, the temperature rises quickly. The height which the temperature attains is frequently not appreciated. Of 46 cases treated in the North Carolina Baptist Hospital from 1942 to 1947, three fourths had temperature peaks above 104°F (40°C). Almost half had temperatures above 105, and 5 patients had peaks higher than 106°F (41.1°C). Hyperthermia may be a poor prognostic sign, though all five of our patients with temperatures of 106 or above survived. The character of the temperature curve was high and spiking with irregular morning remissions—often as much as 3 to 5°F—in 28 cases, high and sustained in 11, and moderate or low in the remainder. In general, children tend to run higher temperatures than adults.

Usually the maximum temperature will be reached during the second week of the disease, anywhere from the seventh to the fourteenth day. With recovery, the temperature usually falls by lysis after a febrile period varying from two to three weeks. A secondary rise in temperature after one peak has been attained frequently heralds the development of a complication, usually pneumonia.

At the onset and early in the course of the disease the pulse is full and strong, but as the disease progresses it may become weaker or even thready. In adults the pulse, in general, tends to parallel the temperature or run slightly below it, no adult in the Baptist Hospital series had pulse rates above the corresponding

temperature. The majority of children below the age of 15 had a pulse rate higher than the temperature; in only about 15 per cent of the children in the Baptist Hospital was the temperature higher than the pulse. A relatively high pulse rate from the onset is often an unfavorable sign. A sudden elevation in pulse rate within a twenty-four hour period usually indicates the appearance of a complication—circulatory failure; in our series the development of pneumonia did not cause the pulse rate to rise. A terminal rise in the pulse rate was observed during the last one to three days of life in approximately a third of our fatal cases.

The *respiratory rate*, at first, is normal or only slightly increased. A slight, nonproductive, bronchial type of cough is frequent at the onset, and is probably caused by organisms settling out in the filter bed of the lungs. Rales may develop later in the disease as a result of true rickettsial pneumonia, pulmonary interstitial edema, or secondary bacterial pneumonia. Near the peak of the disease, pulmonary congestion may occur as a result of myocardial failure.

The *blood pressure* is usually normal at the onset, but later becomes variable. The pulse pressure frequently tends to decrease, with a concomitant drop in both the systolic and diastolic levels, as the peak of the disease is reached. The blood pressure may drop suddenly if peripheral circulatory collapse develops or a massive hemorrhage occurs.

When the patient is first seen, he is usually dehydrated, with a hot dry skin and a parched red tongue. Patients who are moderately or severely ill present a puffy appearance which may be generalized or may be limited to the periorbital region, the face, or the extremities, it is due to edema, which is often difficult to detect early except by laboratory methods. As the disease progresses, the edema becomes more widespread and more pronounced. Most of the time the edema does not pit and does not tend to settle in dependent areas. In severely ill patients, some degree of cyanosis will usually be seen.

The neck is often slightly stiff, and Kernig's sign may be present. The conjunctivae are frequently suffused early, and the patient turns away from the light. Severe prostration, mental confusion, dulling of the senses, restlessness, and hyperesthesia of the skin and muscles may be found early. As prostration increases, the patient becomes lethargic. Muscular twitching, fibrillary tremors and abnormal neurologic signs, such as ankle clonus or a positive Babinski reaction, may appear.

The spleen becomes palpable late in the first week of the disease, and is usually firm and slightly tender. The liver may be palpable, but is rarely tender, jaundice may occasionally be seen, but is not marked except in fatal cases. Distention and constipation usually occur, although peristalsis is not abolished.

Course

The clinical course varies from abortive and mild infections in which the patient may remain ambulatory to fulminating cases leading to death within three to five days. In such instances, the body defenses are overwhelmed by the toxemia of the infection. In most fatal cases, death occurs between the ninth and fifteenth days of rash; patients rarely die after the fourteenth day. Near the peak of the

disease the patient frequently becomes comatose, and neurologic signs are more prominent

Occasionally, after improvement has apparently begun, a recrudescence of symptoms will occur and a new crop of skin lesions will develop, exactly as in typhoid fever, such recrudescences are not common, however

Complications usually become evident by the time the disease reaches its peak in the middle of the second week of rash, they are discussed in detail below Convalescence is slow, and complete recovery may not take place for weeks, months, or as long as a year, even in a relatively mild infection The sequelae are discussed under "Prognosis"

The course of the disease in recently immunized individuals (or those given suppressive chemotherapy) may be atypical and often bizarre (12) The usual time relationship between exposure and the appearance of signs and symptoms, the duration of the disease, and the development of serologic evidence of infection are often greatly altered The multiple crops of skin lesions frequently seen, and the irregular fever reflect the attempts by the parasite to break into the blood stream and to establish itself in new cells

Pathologic anatomy

Rarely in any disease are the pathologic lesions correlated so closely with the clinical picture in the patient during life The gross appearance of the specimens at autopsy often is not impressive Since the disease is one which diffusely involves the smallest blood vessels, the lesions are found in the microscopic preparations A careful study of the patient's clinical record will reveal a very close correlation between the microscopic findings and the physiologic disturbances, although the latter may be out of all proportion to the visible anatomic lesions

Gross lesions are found predominantly in organs derived embryologically from ectodermal structures (16) The skin, in addition to the rash, may show areas of necrosis and gangrene resulting from interference with the arterial blood supply or from ischemia caused by pressure over bony prominences The central nervous system grossly may show few lesions in comparison to the clinical neurologic disturbances, the damage to the brain, however, is greater in spotted fever than in any other rickettsial disease

Fluid exudates into the serous cavities, as well as the edema of subcutaneous and other less firmly organized tissues, reflect the physiologic disturbance in the circulation In general, pulmonary changes are not striking when death occurs within the first ten days of the disease, later, congestion and serous exudation are almost regularly present, often with areas of consolidation

In about one third of the cases the liver shows distinct swelling, cloudiness, and opacity of the parenchyma The cut surface may have a nutmeg appearance or a yellowish color, occasionally with subcapsular streaking, but no softening or focal areas of necrosis are noted grossly The spleen is regularly enlarged, the splenic pulp is firm and tends to bulge from the cut surface, but in cases of long duration it becomes friable

The kidneys are usually normal in size, although the parenchyma may be con-

gested and slightly swollen. The cortex is usually pale and rather opaque; petechial hemorrhages may be noted beneath the capsule, but more frequently they are seen in the medulla and pyramids. The heart is generally of normal size. Any dilatation observed is usually confined to the right ventricle or right auricle. Petechiae are noted more often under the epicardium than elsewhere. Many times the muscle of both ventricles feels flabby, in spite of the vascular character of the disease, however, no areas of thrombosis and necrosis simulating coronary occlusion or myocardial infarction have been described.

In about half the cases purpuric foci are seen somewhere in the mucosa of the gastrointestinal tract. One of the 5 patients on whom autopsy has been performed in the North Carolina Baptist Hospital died from a fatal gastrointestinal hemorrhage which arose, to judge by the character of the blood in the stools, from the lower part of the small intestine or from the right colon, no gross lesion was observed at autopsy, however.

Microscopically, the skin and subcutaneous tissues are the best locations for study of the lesions in the blood vessels, and rickettsias can be demonstrated there most easily. Detailed descriptions of the lesions are given by Wolbach (17). The rickettsias first invade the nuclei of endothelial cells in capillaries, where they multiply in great numbers and destroy the cells. From there the lesions extend centripetally along the intima into slightly larger vessels (the arterioles), where smooth muscle cells of the media are also invaded and destroyed—a distinctive feature of the Rocky Mountain spotted fever strain of rickettsias. Extension into larger blood vessels—arteries—occurs to a greater extent in spotted fever than in the other rickettsial diseases, in which vessels larger than arterioles are rarely affected. The venules are involved to a much smaller extent. The lymphatics are not attacked.

With the death of cells, necrosis occurs in the intima and media of the vessels, resulting in thrombosis and extravasation of blood. The thrombi are hyaline and are composed of cellular and nuclear debris, rarely of fragmented or intact neutrophils. As a result of the thrombosis microinfarcts are formed, chiefly in the skin, subcutaneous tissues, and central nervous system. The rash in the skin and the petechiae seen in internal organs are the result of extravasation from the necrotizing lesions.

The proliferative character of the vascular lesions, as indicated by the presence of numerous mitoses in cells and by perivascular accumulations of mononuclear macrophages, has perhaps not been sufficiently stressed. Indeed, in one case seen at autopsy in the Baptist Hospital series—a child of 4 years dying on the eleventh day of rash—the lesions were strikingly similar to those described in periarthritis nodosa. While it is true that this particular patient had received therapeutic antiserum and that similar changes have been described in serum sickness, lesions of the same general character can be found in cases which have not received specific immune therapy.

In specific organs the diffuse character of the microscopic lesions reflects the fact that the most widely distributed blood vessels—the capillaries—are the site of the first localization of the rickettsias. Areas of demyelination, without cel-

lular infiltration or exudation, can be found in the central nervous system in association with arterioles, or slightly removed from them. The focal lesions or "nodules" in the brain and meninges result from the proliferative reaction.

In the lung, the bronchi are often filled with pus and surrounded by pneumonic involvement in which gram-positive cocci in fair numbers can be stained. Small areas of interstitial infiltration, with some inflammatory reaction, can be found in the myocardium, usually related to the smallest arterioles or to capillaries. In patients dying in the second week of the disease, cellular infiltration is more marked in the epicardium and the adjacent muscle.

In the liver, congestion is associated with the accumulation of fine fat droplets in the cells of both the central and the periportal areas, occasionally, a few scattered minute focal necroses are seen. The involvement of the generative organs frequently noted in Rocky Mountain spotted fever is an unusual feature of rickettsial diseases, it occurs to a greater extent in males than in females. The reticulo-endothelial system shows some degree of hyperplasia, the character of which is often altered especially in the spleen, by secondary bacterial infection.

The involvement of the kidney is usually confined to scattered nephrons, the lesions being most marked in the region of the convoluted tubules, interstitial and perivascular infiltration by lymphocytes is found. The epithelial cells of the tubules are swollen and finely granular, occasionally containing fine droplets of fat. The location of the lesions in the kidney, as well as in other blood vessels, suggests that the rickettsias settle out of the circulating blood and parasitize endothelial cells in locations where the blood flow loses speed in the transition from arteries to capillaries. Few lesions are found in the adrenals—a fact which confirms the impression obtained from physiologic studies that the circulatory collapse arises in the peripheral circulation.

Pathologic physiology

The physiologic disturbances observed in the patient reflect accurately the anatomic damage caused by the rickettsias. However, the degree of disturbance, especially in the circulation, may be quite out of proportion to the severity and number of anatomic lesions.

In the severe, fulminating infections, where death occurs in the first few days of the disease, the body defenses are overwhelmed by the toxic products of the organisms. The clinical picture may be that of peripheral vascular collapse—"shock"—apparently resulting from dilatation of the peripheral capillary bed and pooling of blood, without alteration in the permeability of capillaries, loss of fluid into extravascular spaces, or edema. Early in the course of less severe infections dehydration and loss of electrolytes from the circulation—as measured by blood chlorides—are common, the dehydration is accompanied by little change in the plasma volume and extravascular fluid (thiocyanate space) unless crystalloids—glucose and saline solutions—are administered in large quantities (18, 19).

As the thrombotic and proliferative phase of the lesion develops, interference with the flow of arterial blood leads to ischemic necrosis, infarction, and the resultant secondary effects of anoxia. Anoxic necrosis, resulting in decubitus

ulcers on the back, may be produced by pressure alone without relation to vascular lesions. Most areas of necrosis and gangrene in the skin, particularly those occurring in the extremities and scrotum, result from vascular occlusions.

The micro-infarcts in the brain disturb the cellular metabolism and produce the clinical picture of encephalitis, convulsions, tremors, loss of memory, and alteration of the reflexes. The hyperesthesia of the skin and tenderness of the muscles (which are quite vascular and show few anatomic lesions) may reflect disturbances in the circulation to peripheral nerves, the responsible lesion is difficult to demonstrate by anatomic techniques, but it is a true peripheral neuritis. The sequelae which persist, such as scars in the skin, loss of memory or mental power, and permanent neurologic changes, mirror the damage in organs which cannot regenerate or adequately repair themselves.

The myocardial damage can be detected by serial electrocardiograms, but is not often sufficient to cause frank congestive failure unless the circulation is overloaded by too enthusiastic fluid replacement therapy (19). The changes in the electrocardiogram which have been observed are similar to those occurring with edema due to beriberi, myxedema, or anasarca from other causes. Pathologically, sections of the myocardium in fatal cases will usually show, in addition to interstitial cellular infiltration, some edema of the muscle fibers, in other fatal cases lesions resembling periarteritis nodosa have been seen in small blood vessels. Two mechanisms may be involved in the myocardial failure—mechanical interference resulting from edema, and anoxia resulting from the involvement of arterioles.

The scattered character of the renal lesions, involving individual nephrons, is reflected in the irregular and slight physiologic renal disturbance, as measured by the usual function tests. The elevation of the blood nonprotein nitrogen early in the course of the disease is due to inadequate glomerular filtration resulting from dehydration, when circulatory collapse is imminent, the low blood pressure further reduces glomerular filtration and increases the extent of the prerenal azotemia.

The involvement of the individual liver cells is reflected by a reduction in some phases of liver function during the third week of the disease and during early convalescence; the fact that the cells are physiologically damaged and not destroyed is proved by the return of complete function in late convalescence. The administration of a high protein diet from the first seems to prevent or greatly reduce the alteration in liver function.

A rough general correlation is observed between the petechial character of the rash, the clinical severity of the disease, and the extent of edema. Apparently the permeability of membranes, especially those comprising the walls of capillaries, is altered progressively as the disease increases in severity, so that water, crystalloids, proteins, and red blood cells are passed. The alteration is greatest near the clinical peak of the disease, between the tenth and fourteenth days of rash, at this time there is a tendency for the plasma volume and serum proteins to drop, the thiocyanate space to rise, and clinical edema to develop. These alterations can be accelerated by the excessive administration of crystalloids alone.

The drop in blood proteins progresses very rapidly. The degree of protein destruction can be followed by serial determinations of the amount of nitrogen excreted in the urine (20). In some children, the amount destroyed daily has been equivalent to 3 to 6 Gm. of protein per kilogram of body weight. It is not known how much of the protein escapes from the vascular tree into the interstitial spaces through the damaged capillaries. In any event, the reduction in the circulating serum proteins, especially in the albumin fraction, lowers the intravascular osmotic pressure and sets the stage for the subsequent development of peripheral circulatory collapse. In addition, damage to the liver may reduce the synthesis of new protein so that replenishment is decreased and destruction is increased simultaneously. Replacement therapy with preformed protein is therefore indicated under certain circumstances.

The alteration in capillary permeability is corrected when recovery begins, the blood volume is quickly restored to normal within one or two days after the temperature drops and the toxic symptoms decrease, but the loss of edema may take as long as a week, and the restoration of circulating blood proteins even longer.

When the quantity of fluid confined within blood vessels and found in the extravascular spaces is compared with the changes in weight of the individual, a disproportion is frequently found. The comparison suggests that the permeability of cells *outside* the vascular tree may also be altered, so that fluid accumulates *within body cells* as well as in the interstitial spaces (19). This excessive hydration of cells may affect the function of organs in which vascular lesions are not pronounced. The observation of stupor, tremor, and medullary respiratory arrest, which is occasionally seen in fatal cases, is clinical evidence that nerve cells are hydrated excessively, the increase in cerebrospinal fluid pressure in such instances is usually less than would be expected if the cerebral edema were entirely interstitial. Unfortunately no technique is available at present for the measurement of intracellular fluid. Regardless of whether the fluid goes into tissue spaces or into cells, the loss from the circulating intravascular fluid lowers the blood volume and precipitates peripheral circulatory collapse.

The mechanism responsible for the alteration in permeability of membranes at the peak of the disease is obscure. The maximum changes in capillary permeability occur at the time when immunity should be rising rapidly and beginning to attain ascendancy over the infection. The alterations usually appear at the end of the second week (the time required for the development of antibodies), and the subsequent clinical improvement would suggest that the immune balance is being tilted. The neutralization of antigens by antibodies—either circulating or fixed to tissue cells—must produce a substance which directly affects membranes. It has been known for years that antigen-antibody reactions liberate a histamine-like substance. That histamine and similar substances alter capillary permeability is readily demonstrated by the production of a wheal when histamine is injected into the skin. Our observations suggest that the antigen-antibody effect involves the general circulation and alters the permeability of the entire vascular tree.

The similarity of some of the microscopic pathologic lesions in cases of Rocky Mountain spotted fever to those of experimental serum sickness is intriguing. In our experience the patients in whom such lesions are most pronounced have been those who have received hyperimmune antiserum. Since immune bodies are found in the globulin fraction of serum, the chance presence of immune bodies to rickettsias in blood or plasma might explain the transfusion reactions observed occasionally in patients with rickettsial spotted fever. The development of antihistaminic drugs raises interesting therapeutic implications which will be discussed further below.

Because rickettsias are located intracellularly, one would expect cellular as well as capillary permeability to be increased. It is known that cells participate in the immune process and are affected by allergic or immune manifestations. An antigen-antibody reaction occurring within the cell might be expected to liberate a histamine-like substance which would increase the permeability of the cell membrane. In patients with spotted fever, it is difficult to obtain an adequate quantity of interstitial fluid for chemical examination by the insertion of needles subcutaneously. In view of the ease with which fluid can be obtained from patients with congestive failure, the suspicion that some of the fluid lost from the circulation may be found *within* cells, as well as between them, is strengthened.

The alterations in permeability are evidently reparable with the full establishment of immunity, this conclusion is based on clinical observation alone, however, since no quantitative data on the degree of immune response have been obtained experimentally. The diuresis which regularly occurs with recovery from infectious diseases, including spotted fever, has been known to clinicians for years, though the mechanism has never been explained. The restoration of capillary and cellular integrity should enable interstitial and intracellular fluids to be mobilized and excreted through the kidney.

The application of these principles to supportive therapy is discussed further below.

DIFFERENTIAL DIAGNOSIS

Prodromal period

The onset is characterized by generalized nonspecific symptoms, of which headache and lumbar backache are outstanding. This type of onset is seen in many systemic diseases, especially those caused by the filtrable viruses. Influenza, measles, encephalitis, and poliomyelitis must be considered early in the course, before the rash develops. The epidemiologic history is the greatest help at this stage. A lumbar puncture will frequently aid in the differential diagnosis.

Rash

The development of chills or chilly sensations suggests a blood stream invasion, which is actually what occurs. The disease at this stage must be differentiated from a septicemia of any other cause. The headache and the hemorrhagic character of the rash, as well as the positive tourniquet test, make it very difficult

to differentiate early spotted fever due to rickettsias from that due to meningococci. In meningococcemia the rash frequently becomes purulent and necrotic in the center within one to two days, bacteria can be stained in material aspirated from the lesions, and can be cultured from the aspirate and from the blood.

The rash in measles, chicken pox, and other similar exanthems may be suggestive of Rocky Mountain spotted fever at first, but the rash of measles rarely becomes purpuric or confluent. In measles it usually appears first in the mucous membranes of the mouth whereas, the rash of spotted fever is seen first in the skin of the extremities.

The severity of the illness, together with the mental clouding, headache, high fever, and bradycardia, may be suggestive of typhoid fever. The rash in typhoid, however, usually appears first on the abdomen, continues to blanch on pressure for several days, does not become so papular or petechial, and maintains a paler rose color.

Endemic flea-borne typhus occurs in the same general areas as spotted fever in the Southeastern states, however, the disease is usually contracted in business establishments in urban areas during the cold months of the year. Endemic typhus is generally a much milder disease than Rocky Mountain spotted fever, but may start with identical symptoms. The rash usually appears first on the chest, abdomen or back, and spreads to the extremities, it usually does not become so prominent nor so purpuric, and is frequently fleeting.

Errors in diagnosis usually occur in the clinically very mild infections or in the fulminating types.

LABORATORY TESTS

For diagnosis

No test is available which will quickly establish the diagnosis early in the course of the disease. A conclusive diagnosis can be made by recovery of the infecting organism from the patient. The *infection test* is the most accurate method of proving the rickettsial etiology, but the results cannot be obtained quickly enough to be of use in planning specific therapy.

The rickettsias are found in the blood throughout the first and part of the second week, disappearing when clinical improvement begins. The parasitemia is heavy in severe cases, but may be quite light in mild ones. Male guinea pigs weighing about 400 to 500 Gm. can be infected by the intraperitoneal injection of 1 cc. or more of whole blood transferred by syringe directly from the patient at the bedside (21). Citrated whole blood and ground blood clot can be used, but are less desirable, plasma and serum are not reliable. If the infection is very mild or if the blood has been drawn late in the course of the disease, 2 to 5 cc. should be used, more than 5 cc. of human blood may be toxic to the animal. In fulminating cases blood removed from the heart within several hours after death will usually be infectious. Blood shipped to a laboratory may not give a positive reaction after several hours in transit.

The temperature of the pig should be taken daily by rectum and the scrotum examined for swelling, reddening, and necrosis. If the reaction is positive, fever

appears in 2 to 6 days, rising for four to five days from the maximum normal temperature of 103.8°F (39.9°C.) to 105°F. (40.5°C.). The severity of the disease in guinea pigs bears no relationship to the virulence of the strain for the patient. In mild guinea pig infections a febrile reaction may be the only indication of illness; in severe cases the animals will die. When there is a definite scrotal reaction, experienced individuals can differentiate the gross lesions from those of endemic typhus, with which they are often confused. Smears from the tunica vaginalis should be made, and will show rickettsias in most cases. If more conclusive evidence is desired, serologic tests can be run on surviving animals, or they may be given an immunity (protection) test by inoculation with a challenging dose of a Rocky Mountain spotted fever strain of rickettsias.

Rickettsias isolated at autopsy from guinea pigs or human patients may be grown in fertile hens' eggs by inoculation of the yolk sac with 0.5 to 1.0 cc of a suspension of ground infected tissue. It is not yet established whether this technique is suitable for primary isolation of the organisms from whole blood.

Although *blood cultures* performed by the usual bacteriologic techniques will not grow the rickettsias, blood should be taken for culture several times daily for two to three days when the patient is first seen. Because simultaneous intercurrent disease, such as tick-borne tularemia, may occur, the blood should be planted on special media containing cystine for *Pasteurella tularensis* and under increased carbon dioxide tension for *Neisseria meningitidis*.

The most widely used confirmatory diagnostic procedure is the *agglutination test* employing a strain of proteus bacilli and the patient's serum (Weil-Felix reaction) (22). The test is not specific for Rocky Mountain spotted fever and does not differentiate between the various rickettsial infections. On the whole, however, it is the most useful and practical test available, although it may fail to confirm unusually mild infections or those in which there is an early fatal termination. The OX¹⁹ strain of *Proteus vulgaris* is usually employed, the patient's serum is serially diluted and its ability to clump a suspension of the organisms is observed.

Agglutinins begin to appear during the peak of the disease or early in convalescence, and the titer rises progressively. Three blood samples should, therefore, be taken: the first when the disease is suspected, another during the second week, and a third during late convalescence. The first sample is seldom diagnostic and is used mainly as a control on the second and third. A titer of 1:160 is highly suggestive, but a titer of 1:320 is the lowest that can be considered definitely diagnostic. A progressive rise during convalescence is as important as the final height of the titer.

The reaction usually will disappear within a year, though the titer may rise again with any subsequent infection which produces fever (anamnesic response). The reaction apparently depends on the presence of an antigen common to rickettsias and the proteus bacillus, one antigen has been found to be a specific soluble substance, probably a polysaccharide.

The *complement fixation test* is a specific reaction for the spotted fever strain of rickettsias (23). The test becomes positive at about the same time as the

proteus agglutination test A specimen of the patient's serum should be obtained as soon as the disease is suspected, and another during convalescence several weeks after fever has subsided If the first specimen gives a negative reaction, a titer of 1:16 or greater in the second is diagnostic Complement fixing antibodies will persist for at least six to eight years The antigen is prepared from the yolk sac of infected hen's eggs and is commercially available, the test is technically difficult and results are dependable only in experienced hands The test will be performed by the United States Public Health Service at the National Institute of Health, Bethesda, Maryland or at the Rocky Mountain Laboratory in Hamilton, Montana

If the organism has not been isolated and serologic confirmatory tests are inconclusive, a *test of the protective power* of serum taken from the patient during convalescence can be carried out in guinea pigs Administration of 0.5 cc of the serum is carried out simultaneously with inoculation with a strain of Rocky Mountain spotted fever rickettsias carried in chick embryos or in other guinea pigs (12)

Theoretically, it should be possible to make a diagnosis in the first few days of the infection, by means of the soluble specific substance known to be produced by the rickettsias and presumably excreted in the urine This substance can be concentrated and utilized as antigen for precipitation tests or other immune reactions against convalescent serum from a patient or guinea pig known to have had spotted fever This technique is similar to that which has been used for typing of pneumococci

No diagnostic skin test has been devised, and no diagnostic aid is given by the hematologic findings

For control of therapy

The *hemoglobin* and *red blood cell count* usually show little change until the disease is far advanced, when a normochromic, normocytic anemia will appear in most cases The low point is reached between the tenth and thirteenth days of rash, and may precede or follow the clinical peak of the disease The hemoglobin may drop to 9 Gm and the red blood cell count to 3,000,000, although a hemoglobin as low as 6.5 Gm and a red cell count as low as 2,500,000 are not uncommon

The decrease in red cells probably is due to the debilitating effect of the disease, it persists too long to be accounted for by an alteration in the distribution of the circulating blood The marked and rapid drop might suggest a hemolytic process, but measurements of pigment in the blood do not support this thesis Destruction of erythrocytes by specific parasitization of red cells has not been demonstrated Extravasation of blood into the tissues and loss in the excreta have not been marked, though clinical tests for occult blood in the stool are frequently positive

In nearly all of the cases treated in the North Carolina Baptist Hospital the *white blood cell count* was below 10,000 in the first week of the disease Early leukopenia, with total counts of 4,000 to 6,000, has been quite frequent, in

such cases a differential count shows a neutropenia. As the disease progresses, the white blood cell count frequently rises above 10,000—more often in the range of 13,000. Peaks above 20,000 or below 10,000 are relatively uncommon, each occurring in about one fifth of the cases. The highest count we have observed was 33,750, the lowest 3,350. When counts above 15,000 are seen they are usually in children (24).

As the disease progresses and leukocytosis develops, an increase is noted in polymorphonuclear cells, with a shift toward the left in the Schilling hemogram. The young cells are mostly of the band and stab type, toxic granulation of the polymorphonuclear cells is frequent. In many cases the leukocytosis is associated with the appearance of secondary bacterial infection or follows hemorrhage. The alterations in the total and differential white cell count are discussed further below.

The *urinalysis* at the onset usually shows no abnormality, although the urine volume may be reduced as a result of inadequate fluid intake or decreased glomerular filtration pressure. A trace of albumin consistent with the degree of dehydration may be present. As the disease progresses, slight albuminuria may appear, possibly as the result of fever, but it persists for only two or three days. Albuminuria was not marked in any case in the Baptist Hospital series; half of the patients had none at any time. In 5 cases there was a 1 plus reaction for albumin, and in 2 the reaction was 2 plus or greater. Occasionally the alterations of acute nephritis (red cells and casts in the urine sediment) are present in addition to albuminuria. Five cases in our series of 46 cases showed small numbers of red cells (2 to 5 per high power field in a centrifuged specimen) for periods of one to three days. Occasional hyaline and granular casts were seen in 8 cases.

The *benzidine test for occult blood in the stool* is frequently positive, occasionally gross bleeding or massive hemorrhage from the bowel may occur as a complication.

The *cerebrospinal fluid* will frequently show alterations which reflect the clinical evidence of encephalitis, although the changes cannot be correlated closely with objective neurologic manifestations (24). In many instances the pressure is normal; in other cases, pressures as high as 300 mg of spinal fluid are recorded. Elevations in globulin, as measured by the Pandy reaction are rare. Quantitative estimations of spinal fluid proteins showed an increase in three of 18 determinations, the maximum level observed was 265 mg per 100 cc. The spinal fluid protein, composed chiefly of the smaller albumin molecule, may indicate that the permeability of the cerebral capillaries to proteins is not markedly increased.

The spinal fluid sugar is usually within the normal range—40 to 60 mg per 100 cc. The spinal fluid chlorides are usually in the range of high normal values—100 to 118 milliequivalents per liter (584 to 688 mg per 100 cc). In almost every lumbar puncture in the Baptist Hospital series small numbers of red blood cells—from 1 to 20 per cubic millimeter—were found in the spinal fluid on taps performed without trauma. The white blood cells, predominantly small mononuclears, were found increased in 5 instances, numbering from 10 to 22 cells per cubic millimeter.

For the first few days of the disease, *blood chemical determinations* are most often

within normal limits. As the disease progresses, profound alterations in electrolyte balance and in protein metabolism usually occur (18, 20). The decreased intake of fluid and food, and the increased sweating caused by fever are reflected by a drop in blood chlorides, which may reach levels below 80 milliequivalents per liter (468 mg per 100 cc). The carbon dioxide combining power is usually not greatly altered. With dehydration and a decrease in the urinary output, the nonprotein nitrogen rises, occasionally exceeding 85 mg per 100 cc. When the urinary output becomes adequate, the nonprotein nitrogen drops, reaching normal levels by the time convalescence begins. The level of the nonprotein nitrogen elevation cannot be correlated with the degree of protein destruction.

The circulating blood proteins, which are usually normal early in the course of the disease, begin to drop during the first week and reach their lowest level late in the second week, about the time the clinical peak occurs. It is not uncommon for the total serum proteins to fall as low as 4 to 5 Gm per 100 cc. The serum albumin falls to a greater extent than the globulin fraction, and frequently drops below 2.5 Gm—a level frequently said to be critical for the formation of edema. In addition to the depletion of the tissue stores, which is shown by the drop in circulating blood proteins, a marked destruction of body proteins is reflected by the greatly increased excretion of nitrogen in the urine. The equivalent of 3 to 6 Gm of protein per kilogram of body weight may be recovered daily as urinary nitrogen.

Increased *capillary fragility* can usually be demonstrated qualitatively by the application of a blood pressure cuff; it can be measured quantitatively by a simple suction technique utilizing glass syringes and a manometer.

The *blood platelets* are within normal limits and apparently are not responsible for the hemorrhagic phenomena.

The *prothrombin time* is usually normal early in the course of the disease, although it may become elevated later. Usually an abnormal prothrombin time will revert to normal following the administration of vitamin K. In one instance, however, the prothrombin time remained above 2 minutes and 30 seconds for five days in spite of the daily parenteral injection of 4 mg of vitamin K; it reverted to normal with convalescence. The defect in prothrombin formation is apparently associated with liver damage.

Serial *liver function studies* have been performed on 16 patients in the Baptist Hospital series. The serum bilirubin, as measured by the van den Bergh test, was elevated in only one instance—a case in which other tests also showed evidence of extensive liver damage. In 5 cases a bromsulfalein test showed retention of the dye. The galactose tolerance test was within normal limits in all cases. The changes in the albumin globulin ratio and prothrombin time, discussed above, may indicate some impairment in the synthesis of proteins. Alterations in the conjugation and excretion of bippuric acid were noted after oral or intravenous administration of sodium benzoate. This defect usually occurred during the third week, just after the clinical peak of the disease or in early convalescence. In all cases, all hepatic functions returned to normal during late convalescence. A high protein diet will afford protection against liver damage.

Phenolsulfonphthalein excretion tests of *kidney function* usually fall within

the range of normal. Urea clearance tests are usually normal (70 per cent or better) or they may fall within the range of slight or questionable impairment of renal function, with a clearance of 50 to 70 per cent. Occasional patients (3 out of 16 in the Baptist Hospital series) show definite evidence of renal damage, with a urea clearance of less than 50 per cent.

The *electrocardiogram* shows nonspecific changes in T waves which are similar to those found in myxedema, beriberi, or edema of any kind. Prolongation of the P-R interval and other changes which can be confused with rheumatic fever have been infrequently observed. The changes usually revert to normal during convalescence.

Serial determinations of the circulating blood volume by the Evans-blue technique reveal a normal blood volume (3400 cc. of plasma for a man weighing 70 Kg. or 150 pounds) early in the disease. A transient diminution is seen in severe cases at the clinical peak of the disease (between the twelfth and fourteenth days of rash), with a return to normal during the period of lysis (19). The degree of alteration may be as much as 15 to 20 per cent of the control value. In mild or moderately severe cases, the blood volume may not be significantly altered. Indeed, where no defect in capillary permeability exists, the blood volume may actually be increased if fluids are given to excess; this situation is of more than academic interest, since the plethora may overload the myocardium and set the stage for the precipitation of central circulatory (congestive) failure.

Determinations of the extravascular fluid space following the injection of sodium thiocyanate show a gradual increase from the first week to a maximum at the clinical peak of the disease (19). The amount of fluid in the extravascular space may increase to almost twice the normal value of approximately 13,500 cc. for a man weighing 70 Kg (150 pounds). After the fever begins to subside, the fluid is gradually mobilized and excreted, and the thiocyanate space returns to normal during late convalescence.

The *levels of specific chemotherapeutic agents in the blood* should be followed when such agents have been administered. The blood level of para-aminobenzoic acid (PABA) can be determined by the techniques used for sulfonamides. Because of the rapid excretion of the drug, blood should be drawn within 30 minutes after the administration of a dose. Serum levels of antibiotics can be measured by biologic or spectrophotometric techniques, but the accuracy of the determinations and the correlation of the blood levels with clinical response are not yet completely worked out.

Bacteriologic cultures of blood and sputum for the common gram-positive cocci which secondarily invade the lungs should be made to determine the necessity for antibiotic therapy in the treatment of complications.

For prognosis

In the Baptist Hospital series, we were unable to predict the ultimate clinical severity of the disease or the outcome from either the *total or the differential white blood cell count*. Severe or fatal cases may show either a low or a high total count. A marked rise in the total count frequently, but not always, heralds the development of a complication.

In the differential count, the percentage of nonsegmented polymorphonuclears is usually highest near the clinical peak of the disease. Reversal of the usual ratio between the segmented and nonsegmented forms is not common, with recovery, the nonsegmented forms return to low levels. The most constant alteration is a rise in small lymphocytes concomitant with clinical recovery. This rise occurs regardless of the total white blood cell counts throughout the course of the disease. Indeed, the rise may produce a relative neutropenia, and lymphocyte counts of 60 to 70 per cent are encountered.

Alterations in the percentage of monocytes are not remarkable, though occasional patients will have a single count of 10 to 15 per cent. Eosinophils usually tend to disappear during the acute phase of the disease and reappear with defervescence. Counts above 2 per cent have not been seen in the absence of serum sickness. The only fatal case in which eosinophils were present was that of a patient who died from a massive hemorrhage after the fever had begun to drop. Basophils also tend to disappear during the acute phase of the disease, they appear with surprising frequency in the range of 1 to 3 per cent during early convalescence.

The *sedimentation rate* remains elevated and is of little aid in estimating the prognosis or detecting the development of complications.

A delay in the appearance of *agglutinins* for proteus OX¹⁹ or the *complement fixing antibodies* is not sufficiently dependable evidence on which to base a poor prognosis. Patients may exhibit clinical recovery before the immune titers have reached significant levels.

On the whole, clinical evaluation of the degree of toxicity, the extent of the hemorrhagic phenomena, and the amount of edema has been more helpful than any simple laboratory procedure in estimating the prognosis.

TREATMENT

Specific therapy

Rocky Mountain spotted fever presents an extremely difficult therapeutic problem. Until the diagnosis is definitely established by the appearance of the rash, therapy should be expectant. The prophylactic administration of specific serotherapy and chemotherapy after tick bite and before the development of clinical signs has not yet been shown to be effective. Specific therapy is most efficacious if it can be started at the earliest sign of rash, its value is progressively diminished after the first week of the disease.

Serotherapy. An effective hyperimmune rabbit antiserum, processed to concentrate the immune bodies in the globulin fraction, is commercially available (25). Full therapeutic doses of serum given soon after the rash appears usually lessen the clinical severity of the disease and reduce the toxemic symptoms, though the beneficial effects are somewhat transient. The recommended dose is 1 cc per kilogram (or 2 pounds) of normal body weight. It is intended for intramuscular administration, though it can safely be given intravenously. In our experience with the serum, best results have been obtained when this dose is repeated daily for three days and when the initial dose is given before

the third day of rash, if begun after this time, serum therapy causes little, if any, clinical improvement (30).

In some instances the rash is markedly altered by serum therapy, this alteration may indicate a lessening of the vascular damage. On theoretical grounds one would expect that the serum might prevent vascular damage and leakage of protein into tissue spaces. In our limited experience, serum treated patients have had less edema than patients treated with supportive therapy alone. The administration of antiserum, however, does not prevent alterations in the total serum proteins and the albumin-globulin ratio.

Though the processing of the serum reduces the number of allergic reactions, a skin test or a conjunctival test for hypersensitivity should be given before it is administered. Serum sickness may develop in the second week after injection and produce urticaria, joint pains, and a rise in fever accompanied by eosinophilia. The discomfort can be reduced by aspirin given orally and adrenaline injected subcutaneously; in some instances antihistaminics by mouth or the intravenous administration of a 1 per cent solution of procaine is effective in relieving the symptoms.

The development of potent antibiotics, such as those discussed below, may relegate serum therapy to use only in extremely toxemic patients or in those who have an idiosyncrasy to chemotherapeutic agents.

Chemotherapy Since the rickettsias are located intranuclearly, the ideal chemotherapeutic agent should be able to penetrate two cell membranes of the parasitized host cells. An agent which could be administered prophylactically after a history of tick bite in an endemic area, or early in the course of the disease before the rash is fully established during the stage of heavy parasitemia, would not have to penetrate cells. As yet no chemotherapeutic agent has been developed which is completely effective in all stages of the disease.

The goal of chemotherapy is the development of a rickettsiocidal drug. *Heavy metals* (arsenic and mercury), as 0.3 Gm. of neoarsphenamine dissolved in 10 cc. of a 1:1000 solution of metaphen in water, have been given once daily at three to four day intervals, but the results are not dramatic (26).

All sulfonamides are definitely contraindicated throughout the course of the disease, since their administration to human beings, as well as to experimental animals, has increased the severity of the illness.

Discovery of the harmful effects of the sulfonamides in Rocky Mountain spotted fever led to the clinical trial of *para-aminobenzoic acid (PABA)*, one of the B complex vitamins, which is antagonistic to the sulfonamides in the test tube. PABA inhibits the growth of rickettsias *in vivo*, but a very large amount of the drug is required. The drug apparently activates an enzyme necessary for growth and accelerates cell metabolism by increasing respiration. As a result the rickettsias suffer in the competition with the host cells, and multiplication of the organism is thought to be hindered. The drug has been found to inhibit the growth of the organism in chick embryos and to be effective therapeutically in guinea pigs infected with Rocky Mountain spotted fever.

For children, *para-aminobenzoic acid* should be given in a dose of 1 to 2 Gm. per kilogram of body weight daily (27). Small children should receive the higher

dose, large children the lower dose, and children of intermediate size a dosage in between the two. The daily dose should be divided into twelve equal portions, administered on a two hour schedule day and night. For adults of average size (150 pounds) the initial therapeutic dose is 4 to 6 Gm, followed by doses of 2 to 3 Gm every two hours. It is probably wise to restrict the total daily dosage in an adult to a maximum of 30 Gm daily for a period of not more than one week.

Blood levels of 30 to 50 mg per 100 cc should be attained, in some instances a level of 60 mg per 100 cc may be necessary to obtain a favorable response. If definite improvement is not noted within 48 hours, the dose should be increased to a point which will produce a blood concentration approaching, but not exceeding, 60 mg per 100 cc. The blood concentration may build up if the urinary output is restricted. In most of the reported cases where treatment with PABA was begun early in the course of the disease, a beneficial effect has been noted within 48 to 96 hours. The effect is much less dramatic when the drug is given late in the course of the disease (after the seventh day of rash).

The powdered drug is flocculent and does not dissolve readily in ordinary liquids. When suspended in water and administered through a stomach tube, it tends to clog up the lumen. The acid is available in tablets of 0.5 Gm, but these must be crushed and administered by tube to comatose or severely ill patients. Since the drug is a weak acid, its administration in a chilled 5 per cent solution of sodium bicarbonate (10 cc per gram of PABA) has been recommended, especially in children, where an inherent tendency toward acidosis exists. The powder is more soluble in an alkaline medium, it is more palatable if suspended in fruit juice, which in itself has some alkalinizing power. The acid cannot be given parenterally.

Tablets containing 0.5 Gm of the sodium salt of PABA are also available. The salt is much more soluble than the acid, and its use makes it unnecessary to administer alkalis simultaneously. However, the amount of sodium contained may be sufficient to precipitate edema or to increase any which may already be present. It should be given in the same dose as the acid. Ampules containing 5 cc of a 20 per cent solution or 100 cc of a 10 per cent solution have been prepared for intravenous administration to comatose patients. Vials containing 2 or 5 Gm of the powdered salt have been furnished us for preparation of an intravenous solution, or for use with a gavage tube.

When PABA in either form is given, the carbon dioxide combining power of the blood should be checked frequently. Since the drug has a tendency to produce mild leukopenia, the total white blood cell count should be determined daily during its administration. PABA may cause abdominal distention, delirium, and other toxic symptoms which usually disappear quickly on withdrawal of the drug.

The administration of the drug should be continued for several days after the temperature has returned to normal. The optimum duration of therapy is not yet known, it is possible that the drug should be continued for the duration of the expected febrile period—through the fourteenth day of rash, the two hour schedule should be maintained, though the dose may be reduced.

PABA probably has some effect on the host as well as on the parasite, its

chemical structure is related to that of salicylates, which are known to exert their therapeutic action on affected tissues. If the drug does increase cell metabolism, the principles of supportive therapy outlined below must be followed even more closely.

Antibiotic therapy The antirickettsial activity of many antibiotics has been evaluated. Penicillin is moderately effective against rickettsias in eggs, but in animals it appears to have little or no effect. Streptomycin has proven of no value. Aureomycin, an antibiotic of the same general family as streptomycin, gives promise of developing into a very useful drug for the therapy in rickettsial spotted fever (28). In chick embryos aureomycin is highly effective against most strains of rickettsias. It is still more active in guinea pigs, even if it is given late in the course of the infection. Aureomycin apparently has the property of penetrating cell membranes and attacking rickettsias within cells.

The drug appears to be relatively nontoxic, and can be given parenterally or orally. It is supplied in capsules of 250 mg. for oral administration and in ampules containing 50 mg. of the lyophilized drug as the hydrochloride for parenteral injection. The best method of administration and the optimal dosage are yet to be completely worked out. At this writing the daily oral dose seems to be 50 to 100 mg. per kilogram (3 to 6 Gm. daily for an adult), given on a four to six hour schedule. Since alkalis very rapidly inactivate the drug, none should be administered by mouth for at least two hours after an oral dose of aureomycin.

The parenteral dose of aureomycin should probably be in the range of 5 to 10 mg. per kilogram per day. The drug is unstable in solution. If maximum potency is to be assured, buffered aureomycin should be freshly prepared from the powdered drug for each parenteral dose. Parenteral injections are somewhat painful, since the drug is buffered on the acid side. The discomfort can be reduced without loss in potency by the addition of 0.5 cc. of a solution of 1 per cent procaine to each parenteral dose.

Aureomycin is excreted slowly through the kidney, and appreciable blood levels can be detected for six hours after a single injection. Serum levels can be determined by an assay method which employs a spectrophotometer to measure the growth of a standard strain of staphylococci known to be inhibited by the drug (28). Since the drug is apparently rickettsiostatic and acts by reducing the number of organisms in the body to a point where a low degree of immunity is clinically effective, administration should be continued for two to three days after the temperature is normal.

In severe cases, treated early in the course of the disease, a fall in temperature has been noted within two to three days. The patient becomes less toxemic as the fever subsides and the rash begins to fade. The clinical response in extremely ill patients treated late in the course of the disease is not so dramatic as in those treated earlier, but is still superior to that obtained with any other treatment previously tried.

Aureomycin is easier to administer than PABA, the six hour schedule is much more convenient, and no difficulty is encountered in giving the drug through a duodenal tube if the patient is being fed by gavage. In view of the laboratory

evidence of the effectiveness of aureomycin against the usual secondary invaders, which commonly cause fatal bacterial pneumonia, simultaneous administration of any other antibiotic, such as penicillin, should not be necessary. In our experience to date, complications have been less numerous than with any other type of therapy. Large, loose stools are noted whether the drug is given orally or parenterally. With some lots of the drug nausea or vomiting has been noted, requiring a simultaneous hypodermic injection of atropine with each dose.

Since aureomycin has so far seemed to be of low toxicity, it apparently would be safe to institute therapy on suspicion of rickettsial spotted fever. Time is of the greatest importance in preventing severe complications of the disease, and it is apparently safer to administer the drug erroneously to a patient suspected of having the disease than to allow a full-blown case to develop.

Chloromycetin, another antibiotic similar to aureomycin, has also apparently proven effective in the treatment of Rocky Mountain spotted fever (29). It, too, is well absorbed from the gastrointestinal tract and is apparently of low toxicity. Vomiting has been encountered, but no diarrhea has yet been observed. It is furnished in the form of tablets containing 0.25 Gm. The drug has a bitter taste which can be disguised by pulverizing tablets and suspending them in a sweetened vehicle.

The proper dosage of the drug, the schedule of administration, and the duration of treatment are yet to be determined. The initial dose employed at this writing is 75 mg. per kilogram of estimated body weight, administered in two or three parts at intervals of approximately one hour. After the initial dose, the drug is given at three-hour intervals day and night in doses of 0.25 Gm. for children and 0.5 Gm. for patients above 16 years of age.

The inoculation of guinea pigs with blood from patients treated with the drug suggests that the parasitemia disappears by the second day of treatment. In all cases reported up to this time, therapy with *Chloromycetin*, irrespective of the height of the preceding fever, the age of the patient, or the stage of the disease, has been followed by a fall of temperature to normal levels within 76 hours after the initial dose; the average duration of fever has been between two and three days. A much larger experience with the use of this antibiotic is necessary to demonstrate whether a brief course of treatment is adequate to eliminate completely the rickettsial infection. No recurrences or recrudescences have been observed to date, however.

The administration of PABA suppresses the development of fever and scrotal reaction in infected experimental animals; rickettsias appear in the circulating blood at the same time as in untreated animals (30). Immunity is not affected, since complement-fixing antibodies appear in treated and untreated animals at the same time, and the rise in titer during convalescence is similar in both groups. There is some evidence that the administration of an antibiotic, such as aureomycin, early in the course of a rickettsial infection may suppress or delay the antibody response, as measured by the complement fixation reaction. This retardation or suppression of immunity can probably be explained by the fact that the reduction in the number of infecting organisms early in the course of the

disease provides inadequate antigenic stimulation. It may, therefore, be difficult to confirm the diagnosis by serologic methods, and protection against subsequent reinfection may be much less than after a full febrile course.

The decrease in the period of prostration and convalescence before resumption of normal activities tends to offset the current high cost of therapy with these antibiotics. It may be found that a combination of aureomycin or Chloromycetin with PABA will be even more effective than either drug alone.

Supportive therapy

In uncomplicated cases, diet and good nursing care are the most important factors in supportive therapy, which is directed at the maintenance of nutrition and the prevention of cardiovascular complications and pneumonia. The patients who are dehydrated at the time they are first seen, especially those who have elevated blood levels of nonprotein nitrogen or low blood chloride levels, should be given calculated amounts of an isotonic solution of sodium chloride until the urinary flow returns to normal. Those patients who have nitrogen retention but normal blood chlorides should be given a 5 per cent solution of dextrose in water. If the carbon dioxide combining power is low, sixth molar sodium lactate solution should be administered. The fluids may be given intravenously or subcutaneously, but no single injection should contain more than 20 cc. of fluid per kilogram of body weight. If fluids can be taken orally, the same effect can be achieved with less danger of precipitating pulmonary edema.

Because of the alterations in protein metabolism, the intake of proteins should be increased as soon as the disease is suspected, in order to prevent the development of a full blown protein deficiency. Any type of nutritious food in easily digested form is satisfactory. The daily diet should contain 4 to 6 Gm. of protein per kilogram of normal body weight, depending on the age of the patient and the clinical severity of the disease. Because damage to the liver occurs in moderately severe or severe cases, the diet should also be low in fat and high in carbohydrate. Unless an adequate caloric intake is maintained, marked muscular wasting, with loss of weight, occurs as the disease progresses. The loss of flesh is usually masked by the generalized interstitial edema during the acute phase, but becomes evident during convalescence. Even children, whose metabolism is normally higher than adults, will not only maintain their weight, but may actually gain weight during the illness if supportive therapy is adequate.

In the first days of illness the patient will take food and fluid by mouth. If he becomes delirious, comatose, or uncooperative and the desired intake is not attained, the diet should be supplemented or replaced by liquid feedings with a high protein content. Most children are unable to take the amount and type of food required and should receive gavage feeding as soon as they refuse the diet. This procedure tires the patient less than prolonged attempts to feed him a general diet, and saves nursing time. If necessary, either adults or children can be maintained for days with gavage feedings given every two hours through a large caliber nasal tube left constantly in the duodenum.

A formula which has proved satisfactory is as follows: skimmed milk, 850 cc ;

powdered milk, 100 Gm , corn syrup, 75 Gm , concentrated fish oil to furnish 800 units of vitamin D and 2500 units of vitamin A, niacinamide, 25 mg , ascorbic acid, 150 mg , thiamin chloride, 5 mg , riboflavin, 5 mg , menadione, 1 mg , or a water soluble synthetic equivalent, 4 mg This amount contains 115 Gm of protein, negligible fat, 118 Gm of carbohydrate, 932 calories (0.9 per cubic centimeter), and adequate vitamins If the caloric intake must be increased, substitution of whole milk for the skimmed milk will add 34 Gm of fat, the formula will then contain 1238 calories (1.2 per cubic centimeter) The mixture thickens upon refrigeration, and should be warmed to body temperature before administration It has a consistency and flavor similar to malted milk, the addition of chocolate syrup makes it sufficiently palatable to be drunk from a cup The administration of protein hydrolysates, in our experience, has been of no additional value

When gavage feedings are used, the tube should be washed out with water after each administration of food or medicine It is wise to change the tube from one nostril to the other at least every forty-eight hours, the nose and pharynx should be rested several hours before reinsertion

The intake of all vitamins should be increased Vitamins A, B₁, C, and K should be given in full therapeutic doses because of their possible effect on infection, shock, capillary fragility, and the bleeding tendency, respectively Niacin should be given in the form of the amide, since niacin itself (nicotinic acid) may not be methylated in the presence of liver damage The excretion of vitamins has been found to be increased in spotted fever, in fact, the breakdown products of nicotinic acid have been excreted in larger quantities in spotted fever than in any other infectious disease observed in our hospital (31)

As the disease progresses, alterations in capillary permeability become evident The degree of disturbance observed in the blood chemical findings, especially in the nonprotein nitrogen and chloride values, requires attack The administration of glucose and saline will cause the blood chemical values to return to normal, but the altered capillary permeability permits plasma to be washed out (32) The circulating plasma protein may thus be reduced sufficiently to alter osmotic equilibrium further and to allow more crystalloids to remain outside the blood vessels This vicious cycle leads to peripheral circulatory collapse (medical shock) The serum proteins drop precipitously in such instance, the circulating blood volume is decreased, and the available fluid space increased

If the plasma proteins are found to be low or falling rapidly, or if an appreciable drop in systolic and diastolic blood pressures gives evidence of impending circulatory collapse, preformed proteins should be administered Intravenous replacement therapy in the form of purified albumin, plasma, or whole blood increases the intravascular osmotic pressure enough to allow crystalloids to be given safely Not all the replaced protein will be retained in the blood stream, but some crystalloids will be reabsorbed into the blood vessels on the venous side A very large amount of preformed protein may be required to restore the circulating blood volume and blood constituents to normal We have administered as much as 2800 cc of whole blood and plasma in a period of 10 days to a 2 year

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old child weighing 11.7 Kg., and 2500 cc of plasma in 36 hours to a 15 year old boy.

Concentrated serum albumin (25 Gm per 100 cc) is a very powerful osmotic agent and can increase the blood volume 14 cc. for each gram administered. This degree of response is not usually attained in spotted fever, however The advantage of albumin lies in its small bulk and low salt content, though its mode of action is the same as that of the more widely available plasma The high protein diet described above, if administered early in the illness, will reduce the amount of preformed protein necessary for support of the circulation

If the hemoglobin or hematocrit indicates a reduction in red cells, whole blood would be preferred to plasma or albumin If the serum proteins have been maintained by feeding and anemia is still present, or if a gallop rhythm, venous distention, or other signs of myocardial failure are present, settled red cells will increase the oxygen-carrying capacity of the blood and help to overcome anoxia without overloading the circulation, the blood volume is not increased as much by the administration of cells alone as by the use of whole blood

The type and quantity of parenteral therapy given should be governed by clinical judgement and by careful laboratory control The efficacy of supportive treatment should be checked by repeated laboratory determinations to be certain that the desired results are being obtained. In severely ill patients, for instance, the total serum proteins may have to be determined at intervals of three to eight hours during the critical period. It is possible to overload the circulation in comatose individuals by unwisely chosen fluid therapy administered in excessive quantities through an indwelling duodenal tube

Because of the possibility of myocardial damage, the quantity and speed of administration of parenteral fluids should be carefully governed to avoid overloading the circulation and precipitating acute central (myocardial) circulatory failure and pulmonary edema, this danger is greater if albumin is used

Oxygen therapy should be given by a nasal tube, facial mask, or oxygen tent as soon as impending circulatory failure, pneumonia, or myocardial failure is suspected If the administration of oxygen is withheld until cyanosis is deep and the indications obvious, irreparable damage may have been done

In view of the possibility that the defect in capillary permeability is due to the effect of an antigen-antibody reaction, the administration of antihistaminic agents during the first and second weeks of rash might be helpful

Severe headache, extreme restlessness, or increasing drowsiness due to an elevated spinal fluid pressure may be quickly improved by reducing the pressure halfway to the normal level, the puncture should be repeated the following day if necessary. If the optic disc margins are markedly blurred, cisternal puncture would be a safer procedure Hiccup, which is probably due to irritation of the central nervous system resulting from vascular injury, may prove extremely resistant to therapy. Heavy sedation with barbiturates, scopolamine, or other drugs may be necessary Herpes simplex may be troublesome but rarely is dangerous

In the long run, the patient must still cure himself No supportive therapy

will be helpful unless the patient's immuno response can conquer the organism and his powers of repair are capable of overcoming the vascular defect. If in doubt, it is probably better to undertreat than to overtreat the patient.

Nursing care

Nursing care should be directed toward protection of the skin, prevention of pneumonia resulting from inadequate aeration of the lungs, and maintenance of nutrition. Necrosis of the skin may occur over the pressure points in comatose patients, or may develop in areas of severe hemorrhagic rash, meticulous, constant, gentle, and painstaking care must be given to the skin to prevent breaks through which secondary bacterial invaders can enter, or the development of decubitus ulcers. Frequent turning of the patient and the use of a rubber ring will help to prevent the latter complication, turning will also delay the development of hypostatic pneumonia.

Diet and feeding have been discussed under supportive therapy. If the patient has no oral feedings or is comatose, the danger of parotitis should be combatted by swabbing the gums several times daily with the juice of half a lemon in an ounce of glycerine or mineral oil.

Occasionally, as the result of damage to the central nervous system, the patient may sleep with his eyes open. Instillation of some mild protective non-evaporating substance such as cod liver oil will prevent drying out of the cornea and the development of corneal ulcers.

Isolation

Since the disease is of low infectivity to human beings, except through the medium of the tick, strict isolation is not necessary. The patient on admission should be carefully searched for ticks, so that they cannot transfer to the nurse or physician. The blood of the patient early in the course of the disease is infectious if accidentally inoculated under the skin through a needle prick. Even gangrenous skin lesions, however, are not dangerous to another individual, and rubber gloves are not necessary to prevent transmission of rickettsias. Gowns are not necessary. A mask worn by the nurse may prevent the transfer of secondary bacterial invaders to the respiratory tract of the patient.

The excreta, particularly feces, may be potentially dangerous if allowed to dry so that the dust could be inhaled. It would probably be wise to mix an antiseptic with the excreta before disposal.

COMPLICATIONS

Circulatory disturbances

Circulatory failure is most likely to occur between the eighth and fourteenth days of rash, and may be peripheral or myocardial in origin. The mechanism by which peripheral circulatory failure develops and the principles for prophylaxis and treatment have been discussed under supportive therapy.

Myocardial failure may result from the pathologic process or from overloading the myocardium beyond its functional capacity by overzealous fluid administra-

tion. Impending myocardial failure can be recognized by a rise in pulse rate, the development of a gallop rhythm, and an increase in venous pressure, noted first in the neck veins and confirmed by direct measurement in the antecubital vein with a spinal fluid manometer

The presence of a gallop rhythm or venous engorgement is an indication for digitalization. Digitalis should be administered with caution, since a myocardium damaged by infection is probably more sensitive to digitalis than one failing from purely mechanical reasons. If the failure is sudden and is accompanied by pulmonary edema, strophanthin or purified glycosides of digitalis should be given intravenously

Pneumonia

The most serious complication, and the one which most frequently leads to death, is pneumonia. The pulmonary infection may be due to a true rickettsial invasion of the lungs, in this type the sputum will be scanty and not purulent, and the roentgenogram will show diffuse infiltration. If this type of pneumonia develops, irradiation over the lungs could be added to the specific therapy described above

More commonly, pulmonary congestion occurs as a result of generalized interstitial edema. Protein-containing edema fluid furnishes an excellent culture medium for the bacteria ordinarily found in the mouth, and may lead to pneumonia. The full development of pneumonitis can sometimes be prevented by the administration of protein to control the edema, and by frequent turning of the patient. If the edema is on a cardiac basis, the heart failure must be treated.

Since penicillin is a relatively harmless drug, it is probably wise to begin the immediate parenteral administration of 10,000 to 25,000 units of the aqueous solution every two to three hours to patients who exhibit the slightest signs of pulmonary disease. Aureomycin, and possibly Chloromycetin also, are effective against most gram-positive cocci, the simultaneous administration of penicillin is probably not necessary when one of these drugs is given. If bacterial pneumonia develops under aureomycin therapy or does not respond to penicillin, it is most likely due to a gram-negative rod and should be treated with streptomycin.

Necrosis

Gangrene may develop in the distal phalanx of an extremity, in any area of skin, in the scrotum, or in an ear lobe as the result of complete thrombosis of an artery where the collateral circulation is not adequate. The injection of procaine hydrochloride around the sympathetic ganglia may reduce the vascular spasm and improve circulation, control the pain, and prevent the aggravation of restlessness. Spasmolytic drugs with generalized systemic effects, such as Etamon and Priscol, should be used with caution in view of the already existing tendency toward low blood pressure. Amputation or excision and skin grafting may be necessary if other measures fail, but usually can be postponed until early convalescence

PROGNOSIS

In untreated cases

In untreated cases the overall mortality for the United States as a whole has been about 23 per cent for the years 1939 through 1946. The mortality will be altered by the virulence of the local strain. As a general rule, the prognosis becomes increasingly poor with advancing age, the disease is especially severe in individuals past 40 years of age. Topping has calculated the average mortality rate for patients under 40 as approximately 13 per cent, and for patients above that age as about 41 per cent (33).

Vaccination within the year in which the infection is acquired increases the prognosis tremendously. The mortality in individuals who are infected with Rocky Mountain spotted fever in the same year that they were vaccinated has been estimated by Parker at 9 per cent, as compared with 76 per cent in unvaccinated individuals in a comparable area (12). In addition to reducing the mortality, recent immunization decreases the clinical severity of the disease and its duration.

It is difficult to estimate the ultimate prognosis from the appearance of the patient at the time he is first seen. The greater the clinical severity of the disease, the poorer the prognosis. We have classified cases as mild if the tourniquet test is negative throughout the illness, if edema is minimal or absent, and if the pulse and blood pressure remain stable. Moderate cases are those in which the patient exhibits a positive tourniquet test, slight clinical edema, tachycardia, and toxic symptoms. The disease is considered severe if marked purpura, moderate to marked clinical edema, delirium, and other signs of severe infection are present. In our experience the temperature peak and the total or differential white blood cell count have been of no help in estimating prognosis. Complications, especially pneumonia, make the prognosis poorer.

In treated cases

Complications are decreased and the prognosis improved by specific and supportive therapy. The time in the course of the disease at which therapy is instituted will affect the prognosis. If supportive therapy alone is given, early treatment will decrease the number of complications and the extent of the physiologic disturbance. Vigorous supportive therapy in the North Carolina Baptist Hospital series of 46 cases did not prevent 8 deaths—a mortality of 17 per cent, during the same year, however, 92 deaths occurred in 341 cases throughout North Carolina—a mortality of 27 per cent. Because of the discrepancy in the size of the groups the difference may not be statistically significant, but it has been our clinical impression that vigorous supportive therapy has saved individual patients who would otherwise have died, and that in other cases the degree of toxemia has been decreased, and convalescence shortened.

In Topping's experience with 52 serum-treated cases, the initiation of antiserum therapy before the third day of rash has resulted in a reduction of mortality

from the expected figure of approximately 19 per cent (25). The initiation of immune serum therapy after the third day of rash has not altered the ultimate prognosis, though it may make the patient less toxemic.

The results of treatment with para-aminobenzoic acid (PABA) are difficult to evaluate from the reports in the literature (24). Many of the cases were treated in the second week of the disease, and improvement began at about the time it would have been expected in the natural course of the disease. In cases treated with PABA within the first week of the disease the prognosis is fair to good and is better than with supportive therapy alone, after the first week of the disease, PABA probably has little effect on the ultimate prognosis.

Aureomycin and Chloromycetin, on the other hand, appear to be definitely superior to any other therapeutic agents previously tried. The prognosis becomes good in any except the most severe cases if treatment is started in the first week of the disease. Late treatment in the second week improves the prognosis over that expected with supportive therapy, and probably with PABA. Experience with the drugs is too limited, however, to justify an attempt to estimate the prognosis in percentage.

The duration of convalescence is definitely decreased by supportive therapy; it is shortened still more by early treatment with PABA, and is decreased most by aureomycin and Chloromycetin therapy. Because of the wide variation in the severity of individual cases, it is difficult to estimate the shortening in terms of days.

In reinfections

Recovery from Rocky Mountain spotted fever confers a considerable degree of immunity, which is apparently lifelong. Immunity is not complete, however, for second and third cases have been reported. In human beings and guinea pigs treated with PABA antibody formation has not been depressed to an extent that would seem to make reinfection more likely. It is quite possible that early treatment with aureomycin or Chloromycetin may suppress the antigenic stimulus, and hence the immune response, so greatly that reinfection would occur almost as readily in patients who have recovered as in individuals who have never been infected. The protection would be about comparable to that conferred by vaccination the same number of years before.

Recovery from rickettsial spotted fever does not confer cross immunity against endemic flea-borne typhus or other infections with rickettsias that occur in this country. A minimal increase in resistance to other rickettsial diseases as a group can be demonstrated immunologically by proteus agglutinations, and in some instances by cross reactions in low titer to complement fixation tests using other strains of rickettsias as antigen. The degree of possible protection is of little clinical significance, however.

CONCLUSION

Rickettsial spotted fever is one of the most severe and dramatic of the acute infectious diseases. In areas of high endemicity the mortality rate in recent years has exceeded that of the other common infectious diseases.

The introduction of effective chemotherapeutic agents has initiated a new era in the history of the disease. For the first time it is possible to arrest the natural course and to prevent the development of severe physiologic disturbances. The studies which have been done on the marked metabolic and functional changes, especially in the circulation and the metabolism of proteins, may offer some clues to the better understanding of all infectious processes.

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ADDISON'S DISEASE

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I	Introduction	373
A	Patients in the present series	374
1	Evidence of Addison's disease	374
2	Incidence	374
3	Age, Sex and origin	374
II	The clinical picture of Addison's disease	374
A	Aethenia	376
B	Weight loss	377
C	Gastrointestinal manifestations	377
1	Abdominal pain, "Peritonitis like syndrome"	378
D	Pigmentation	379
1	Incidence	379
2	Description Location	379
3	Role of cortical destruction	380
4	Effect of hormone therapy	380
5	Vitiligo	380
E	Cardiocirculatory manifestations	381
1	Arterial hypotension	381
2	Postural hypotension	381
3	Crisis	382
a	Precipitating factors	383
b	Pathological physiology	383
4	Electrocardiographic findings	384
5	Cardio roentgenographic findings	384
F	Disturbance in renal function, electrolyte and water metabolism	385
1	Impaired renal concentration	385
2	Urinary clearance studies	385
3	Basis of renal dysfunction	387
4	Loss of sodium and water in the urine and from extracellular fluid	387
5	Sodium loss through intestines	387
6	Potassium retention	387
7	Effects of DCA on electrolyte and water metabolism	388
8	Sodium chloride excreting hormone	388
G	Disturbance in carbohydrate and protein metabolism	388
1	Hypoglycemic symptoms	388
2	Symptomless hypoglycemia	389
3	Other manifestations of disturbance in carbohydrate metabolism	389
4	Nature of the disturbance in carbohydrate metabolism	389
a	Faulty intake and absorption of carbohydrate	389
b	Disturbance in glycogenesis and glycogenolysis	390
c	Faulty formation of carbohydrate	390
d	Impaired utilization	391
e	Inulin corticosterone antagonism	392
f	Summary	392
5	The carbohydrate active cortical hormones	392

H Manifestations of other endocrine gland dysfunction	393
1 Pituitary gland	393
a Hypopituitarism	393
b Evidence of primary adrenocortical involvement	393
2 Thyroid gland	394
a Hypothyroidism	394
b Hyperthyroidism	394
c Central role of the pituitary	394
3 Gonads	395
4 Pancreas Addison's disease and diabetes mellitus combined	395
a Incidence	395
b Clinical manifestations	395
c Insulin sensitivity	396
d Relationship of the diabetes to the Addison's disease	396
5 Thymus gland and lymphnodes	396
6 Parathyroids	397
7. Panhypocorticalism Addison's disease with multiglandular insufficiency	397
I Neuropsychiatric and neurologic symptoms	398
1 Observations of early students of Addison's disease	398
2 Clinical significance	398
3 Neuropsychiatric symptoms and the delirious state	398
4 Mild neuropsychiatric symptoms	399
5 Marked neuropsychiatric symptoms, Psychoses	399
6 Neurologic symptoms Spinal cord involvement	399
7 Basis	400
a Hypoglycemia	400
b Hypotension	400
c Cortical hormones	400
1 Electroencephalographic studies	400
2 Clinical observations	400
d Organic brain disease	401
III Laboratory findings	401
A Blood electrolytes	401
1 Blood sodium and the sodium deprivation test	401
a Normal blood sodium in cortical insufficiency	401
2 Blood chlorides	402
3 Blood potassium	402
4 Effects of treatment	402
B Blood proteins	402
C Blood glucose, urea nitrogen and other chemical constituents	403
D Hematologic examination	403
E Gastric analysis, Urinalysis	403
F Biopsy of skin	403
G Tests of adrenocortical function	404
1 Estimation of desoxycorticosterone activity	404
2 Glycogenic corticosteroid and 17-keto-steroid excretion	404
3 Response to pituitary adrenocorticotropic hormone	404
a Response to epinephrine	405
IV Treatment	405
A Five phases of development	405
B Treatment of patients in the present series	406
1 Early replacement therapy	406
2 Cortical extracts	406

3 Electrolyte phase	406
4 Desoxycorticosterone	407
5 Combined therapy	408
a Treatment of crisis	408
b Treatment of cerebral manifestations	409
c Maintenance therapy	409
1 DCA requirements	409
2 Pellet requirements	410
3 Pellet implantation	410
4 Pellet depletion	411
5 Re implantation of pellets	411
6 Maintenance with DCA injections	411
7 Use of cortical extract in DCA treated patients	412
d Treatment of coexisting endocrine disease	412
1 Diabetes mellitus	412
2 Hypothyroidism	412
3 Hypogonadism	412
4 Panhypocorticalism	412
e Advantages of maintenance therapy	412
f Shortcomings of maintenance therapy	413
6 Progress in therapy	415
7 Relative value of therapeutic measures	415
8 Future	415
Bibliography	415

I INTRODUCTION

The clinical features and the underlying pathological anatomy of Addison's disease remain essentially as Thomas Addison described them almost a century ago. It is particularly in the treatment of the disease and in the elucidation of its pathological physiology that important advances have been made in recent years. During this period of therapeutic progress, the fundamental aberrations in electrolyte and water metabolism characteristic of adrenal cortical destruction were recognized, and the existence of important disturbances in carbohydrate and protein economy was established. The preparation of potent adrenal cortical extract, the use of sodium salts, the isolation of biologically active crystalline cortical hormones and especially the synthesis of desoxycorticosterone have resulted in a marked and favorable change in the outlook for the Addisonian patient, who may now not only expect to survive the crises of the disease and live longer, but may also maintain a useful existence.

Anatomical studies have defined more precisely Addison's original view concerning the etiological role of morbid changes in the adrenal glands. It has been demonstrated that Addison's disease results from bilateral destruction of the adrenal cortex independent of medullary involvement. Morphological changes have been observed in other endocrine glands especially the thyroid and the anterior lobe of the pituitary. Recently, myocardial lesions which are presumably secondary to hormonal therapy have been described.

Addison's description included the cardinal symptoms of the disease. The neuropsychiatric manifestations have become more fully appreciated in recent years. Symptoms of hypoglycemia, unknown as such prior to the discovery of

insulin, are now known to constitute an important part of the clinical manifestations of adrenal cortical insufficiency. Symptoms due to involvement of other endocrine glands may alter the classic picture of Addison's disease.

The purpose of this paper is to establish the present status of Addison's disease. This will be attempted through a consideration of fifty cases of Addison's disease which were treated at The Mount Sinai Hospital during the past twenty-two years. The bedside observation of these patients, the laboratory data and the pertinent post mortem findings will be coordinated with recent advances in the study of the subject.

A. Patients in the present series

1. *Evidence of Addison's disease* All of the fifty patients considered here exhibited clinical manifestations characteristic of the disease. Post mortem examination in twenty-five cases revealed bilateral adrenal cortical destruction caused by tuberculosis in eighteen and by cytotoxic atrophy in seven cases. The remaining twenty-five patients, including eleven who are still alive, experienced attacks of Addisonian crisis which responded to specific therapy. Blood sodium determinations in 23 of the 25 patients revealed subnormal values. In two patients, admitted in the "pre-salt" era, who died in crisis, the diagnosis rests on clinical findings alone.

2. *Incidence* During the twenty-two year period in which the fifty patients were treated, a total of 306,620 patients was admitted to the Hospital—a ratio of 1:6000. The incidence was higher in the second half of the twenty-two year period. As may be seen from table I, there were more than three times as many cases of Addison's disease in the second eleven year period. This increase in incidence is probably due to a growing understanding of the disease.

3. *Age, sex and origin* There was an almost equal division of cases between the sexes: twenty-four males and twenty-six females. Table II shows the ages of the patients at the time of admission to the hospital, and demonstrates a maximal incidence in the third and fourth decades of life. The youngest patient was eleven, the oldest sixty-two years of age.

Forty-nine of the patients were white, one was an American Negro. Of the former, about half were born in the United States, the others had emigrated from various European countries.

II. THE CLINICAL PICTURE OF ADDISON'S DISEASE

Thomas Addison in his classic essay "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules" (1), published in 1855, described with remarkable completeness the clinical picture of the disease which bears his name. His description, although based on personal observation of only five patients, holds true to this day in the vast majority of cases. It emphasizes the insidious manner of onset and describes the principal manifestations. Addison wrote of "general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin." He spoke of an anemia which does not occur in the sense in which the term is now used.

Infrequently the onset may be sudden, a person apparently in good health may be precipitated suddenly into an Addisonian crisis following an infection

TABLE I
Incidence

YEAR	CASES OF ADDISON'S DISEASE	TOTAL NUMBER OF HOSPITAL ADMISSIONS
1924	1	12,402
25	0	12,647
26	1	12,334
27	1	12,633
28	1	11,570
29	0	11,532
30	0	11,874
31	2	11,650
32	2	12,167
33	1	13,689
34	3	13,797
35	2	14,198
36	5	13,359
37	1	14,749
38	7	15,745
39	3	16,074
40	4	16,726
41	3	16,668
42	2	16,585
43	2	15,986
44	4	15,030
45	5	15,205
Total	50	279,013

TABLE II
Age and sex distribution

AGE GROUP	NUMBER OF PATIENTS	NUMBER OF MALES	NUMBER OF FEMALES
0-10	0	0	0
11-20	5	4	1
21-30	5	3	2
31-40	16	6	10
41-50	16	8	8
51-60	7	3	4
61-70	1	0	1
Total	50	24	26

or an operation for an unrelated condition. One of the cases in Addison's original treatise was described as having been acute in its development and rapid in its course. Usually, however, the patient becomes progressively asthenic, experi-

ences a slow but continued loss of weight, loses appetite, and either becomes himself aware or is told by others of a change in the color of his skin. The very appearance of the patient with Addison's disease often suggests that these symptoms are present.

A. Asthenia

All fifty patients¹ complained of persistent or recurrent progressive weakness, thirty-two patients volunteered this as their first symptom. The asthenia is often obvious, the patient looks and acts fatigued, often even while lying in bed. The speech is frequently slow and languid, and the patient may state that even thinking requires undue effort.

One approach to an understanding of the asthenia is provided by the results obtained with therapy. In many patients there is notable diminution of weakness after the use of sodium salts alone. The addition of desoxycorticosterone acetate results in further improvement and provides relief of this symptom to a greater number of patients. A few patients also require the use of cortical extracts. Despite all these measures, in five of the cases the weakness was not appreciably alleviated. These patients had manifestations of involvement of other endocrine glands.

While the aberration in salt metabolism is of great importance in the production of asthenia, alterations in carbohydrate and protein metabolism also play important roles. Hypoglycemia occurs in Addisonian patients and in adrenalectomized animals. This suggests that the weakness may be due, at least in part, to simple lack of fuel. The administration of glucose to adrenalectomized animals was found to delay the development of symptoms of adrenal cortical insufficiency and to prolong life for a short period (2). Similar treatment proved to be decidedly beneficial in temporarily relieving the weakness of Addisonian patients (3).

More recently, Ingle and Lukens found that the work ability of adrenalectomized rats could be significantly restored by infusions of glucose (4). Ingle (5) had previously shown that, whereas the work performance of the adrenalectomized rat was but slightly improved by the administration of sodium chloride, it was markedly improved by injections of cortical extract containing carbohydrate-active hormones. Ingle also demonstrated (6) that the administration of desoxycorticosterone acetate had a negligible effect in maintaining the work capacity of adrenalectomized rats as compared to the carbohydrate-active corticosterones.

It is difficult to appraise the importance of any one metabolic disturbance in the production of the asthenia. For example, the sodium salts and DCA² indirectly affect the carbohydrate metabolism by increasing the absorption of sugar from the intestinal tract, with a consequent increase in hepatic storage of glyco-

¹ Case histories and data pertaining to many of these patients have appeared in other publications (22), (97), (98), (155), (174), (177), (210), (211), (232).

² The abbreviation DCA will be used frequently henceforth to denote desoxycorticosterone acetate.

gen. Similarly, cortical extract and crystalline corticosterone have a salt-retaining action in addition to their profound effect on intermediary metabolism.

Hypotension may contribute to the production of asthenia as evidenced by the improvement in some patients with adrenalin or other pressor substances. However, sodium salts, alone or in conjunction with adrenocortical hormones are required for lasting improvement.

B Loss of weight

Loss of weight is one of the cardinal symptoms of Addison's disease. All of the patients in the present series had lost weight, one patient lost sixty-five pounds in a year, another, sixty pounds within six months. The smallest loss was ten pounds, and the average was twenty-five pounds. The patient appears to be dehydrated as well as thin. As noted by Addison, the patient is not cachectic despite the wasting.

The following factors contribute to the loss: inanition resulting from gastrointestinal symptoms and from impaired intestinal absorption (7), chronic dehydration secondary to the loss of sodium (8), disturbances in intermediary metabolism, involvement of other endocrine glands—the thyroid, the pituitary and rarely the pancreas, active tuberculosis.

C Gastrointestinal manifestations

Gastrointestinal manifestations were so marked in the first case in this series admitted to the Hospital in 1924 that poisoning was suspected and Addison's disease was recognized only at autopsy. The patient had noted the sudden onset of nausea and vomiting following the ingestion of a meal in a restaurant. Protracted vomiting persisted as the outstanding symptom for two weeks until the patient died in collapse, two days after admission to the hospital. More commonly the patient is first troubled with anorexia of insidious onset which ultimately becomes severe. This is often accompanied by nausea and vomiting, less often by diarrhea. A small percentage (16%) had an increased desire for salty food. The most common symptom in the present series was anorexia, which occurred in 80% of the patients, the most severe was vomiting, observed in 60% of the patients, the least frequent was diarrhea, which occurred in but six of the fifty patients. Several patients complained of persistent anorexia, and a few of recurrent diarrhea, even after the blood electrolyte content and the blood pressure had been restored to normal.

There are experimental and clinical observations which suggest that the anorexia is related to the loss of sodium or to the acidosis which it produces. Allers and Kendall (9) noted that thirty to sixty days after adrenalectomy, dogs developed anorexia followed by persistent vomiting despite adequate sodium chloride intake. The serum bicarbonate in these animals had fallen to thirty volumes percent. The addition of sodium bicarbonate or sodium citrate to the dogs' diet resulted in restoration of their appetites and general well-being. Groat (10) using rats, observed an even more direct relationship of the anorexia to the administration of sodium chloride. He noted that untreated adrenalect-

tomized rats ate but little food, whereas adrenalectomized rats receiving sodium chloride showed a renewed interest in food and maintained a food intake which was within normal range. Parallel results in Addisonian patients are common clinical experiences.

Although increased appetite for salty food occurred in so few patients that its diagnostic value is questionable, experimental observations indicate that this symptom is related to adrenocortical insufficiency. It has been found that adrenalectomized animals prefer a diet containing increased amounts of sodium chloride and that following treatment with cortical hormone the appetite returns to normal (11, 12).

The frequent occurrence of gastric achlorhydria also suggests a relationship between the anorexia and the electrolyte disturbance. The relationship of diarrhea to achlorhydria is well known. The absence of free hydrochloric acid was noted in 50% of the patients in this series whose gastric contents were analyzed, and similar findings have been reported by other authors (13). However, no definite relationship could be established in the present series between the occurrence of gastrointestinal symptoms and the presence of achlorhydria. The administration of dilute hydrochloric acid did not correct the symptoms in all of the patients who had an achlorhydria. In one patient the anorexia persisted even though free hydrochloric acid reappeared in the gastric contents following treatment with DCA and sodium chloride. On the other hand, in the majority of cases all of the gastrointestinal symptoms responded favorably to treatment with salt alone, or salt with DCA or cortical extract indicating that the altered electrolyte metabolism is responsible, to a large extent, for the production of these symptoms.

Other explanations must be sought for the persistence of gastrointestinal symptoms in some patients despite treatment. In one of the patients atrophy of the anterior lobe of the pituitary gland was encountered at post mortem examination, in two patients clinical evidence of multi-glandular endocrine involvement was present. Hyperplasia of the lymphatic elements in the gastrointestinal tract occurs, and pancreatic atrophy has been reported. Mild degrees of hepatic insufficiency have been observed clinically (14), and more marked changes of liver damage have been observed at post mortem examination (15), (16). In the present series the liver was normal in only one of eighteen cases examined histologically.³ Changes commonly seen in many other diseases were noted. These consisted of conspicuous vacuolization of liver cell nuclei, fatty changes within the lobules, leucocytic infiltrations in portal fields, central lobular congestion and atrophy, and focal parenchymal atrophy.

1 *Abdominal pain, peritoneal syndrome*. A few patients complained of vague abdominal pain. One patient had pain similar to that accompanying peptic ulcer, but this symptom disappeared following the use of DCA and salt. Symptoms similar to those encountered in acute peritonitis, including diffuse abdominal

³ The histological data presented in this paper are part of a more detailed study of the morbid anatomy of Addison's disease carried out in collaboration with Dr. Frederick G. Zak.

tenderness, rigidity of the abdominal musculature, hiccough, vomiting and prostration, have been noted by several authors since Ebstein (17) first called attention to a "peritonitis-like" syndrome in the terminal stages of Addison's disease. One patient in the present series experienced protracted abdominal pain, lower abdominal direct and rebound tenderness and fever—a picture highly suggestive of subacute peritonitis. However, autopsy revealed hemorrhagic necrotizing destruction of the adrenals without evidence of peritonitis. It is concluded that the abdominal symptoms were probably due to marked periadrenal inflammation. In two patients the abdominal pain was due to acute cholecystitis, in a third patient to acute appendicitis.

D Pigmentation

1 *Incidence* Pigmentation is the most striking sign encountered in Addison's disease. It occurs in a very high percentage of cases, and was observed in all but one of the fifty patients in this series. In ten patients it was the first symptom noted. However, the presence of pigmentation is not necessarily of diagnostic significance, since a similar discoloration of the skin occurs in other diseases. Although earlier authors (18) frequently reported cases of Addison's disease without pigmentation, more recent reports stress the rarity of such an occurrence. A recent report of Beck et al (19) deals with an instructive case with fatal outcome in which there was complete absence of pigmentation.

2 *Description, location* The cutaneous pigmentation has been described variously as tan, brown, bronze, smoky and negroid. All of these color gradations were observed in the present series. However, the most frequent color described was tan. Several of the patients stated that their pigmentation began as a sun-tan which persisted after the summer had passed, became permanent and gradually darkened. The pigmentation is usually diffuse although the exposed surfaces are often darkest.

The presence of pigmentary changes in unexposed parts of the body is of greater clinical significance. The most important and most frequent⁴ are the poorly demarcated patches of brown-grey, grey-black or blue-grey pigment on the labial mucocutaneous junction, in the mucous membrane of the vestibulum oris, on the gums, on both parts of the palate, and at times also upon the tongue. Pigmentation in the mouth, as elsewhere, occurs frequently in parts subjected to pressure and should be looked for on edentulous gingival ridges and especially beneath dentures. However, similar pigmentation can occur in normal Negroes and in persons of Mediterranean origin.

Pigmentation of diagnostic importance is also found in operative and other scars and in the folds of the axillae, the palms and fingers, and in places where pressure is exerted such as the elbows and the hatband region, or where a restraining or tight-fitting garment has been worn. One patient in the present series, a fifty year old bookkeeper, had pigmentation of the elbows only. There may be increased intensity of the normal areolar, perianal, and genital pig-

⁴ Present in 80% of the cases in this series

E Cardiocirculatory manifestations

The essential cardiocirculatory manifestations were described by Addison in the five cases which he observed. He emphasized the "small and feeble pulse" and the remarkable feebleness of the heart's action consistent with the later described arterial hypotension. The observation in one case of "a kind of fainting fit upon rising to have his bed made" would now be recognized as a symptom of postural hypotension. The symptoms later designated as manifestations of crisis were described by Addison. The heart was noted to be small at autopsy. Roentgenographic and electrocardiographic studies have amplified Addison's findings in this respect.

1 *Arterial hypotension* Over 90% of the patients in the present series exhibited hypotension at the time of admission to the hospital. The blood pressure in Addisonian patients is subject to the same fluctuations on exertion or with excitement, and the same diurnal variation as found in other individuals (23). "True" blood pressure readings were obtained in several patients only by repeating the determination after a five or ten-minute interval, and by taking the pressure at various times in the day. The average systolic pressure, in patients other than those in crisis or undergoing treatment, was 90 mm Hg, and the average diastolic 65 mm Hg, the values in females were generally somewhat lower than those in males. One patient, who gave a history of having had hypertension previous to the onset of symptoms of adrenal insufficiency, had a blood pressure of 140/70 before treatment. Other observers have noted similar findings (23). The indications are that the hypotension depends not only on the degree of adrenal insufficiency, but also to some extent on the patient's previous state of arterial tension. However, all patients in crisis exhibited marked degrees of hypotension.

2 *Postural hypotension* Many patients in adrenocortical insufficiency experience dizziness and faintness with a change in posture, indicating that in addition to the hypotension a postural component is present. This circumstance is emphasized by Ghrist (31) who demonstrated that a decline in both systolic and diastolic pressures took place when the Addisonian patient, placed on an adjustable table, was brought from a reclining to an upright position. Concomitantly there was an increase in pulse rate, a change which Rowntree and Snell (23) did not observe in essential postural hypotension.

Several factors are involved in the production of the hypotension and its postural component. Apart from the possible direct effect of the hormone on the arterioles and the heart, disturbances in the electrolyte and water, carbohydrate and protein metabolism arising from the adrenocortical hormone deficiency are important. Some authors suggest that reduction in the basophilic cells of the anterior pituitary lobe, a frequent occurrence, may contribute to the production of the low blood pressure (125, 126).

Treatment of patients in adrenocortical insufficiency with sodium chloride and water alone or in conjunction with DCA or cortical extracts results in eleva-

tion of the blood pressure. Since this occurs concomitantly with restoration of the fluid and electrolyte balance the latter is undoubtedly important in the correction of the hypotension. A favorable influence on the blood pressure probably also results from the indirect effect of DCA and salt or a direct effect of cortical extracts on nutrition and carbohydrate metabolism. The question of a direct effect of DCA on the blood pressure is raised by the fact that higher blood pressure levels may be obtained in Addisonian patients treated with DCA in addition to sodium chloride than with the latter alone. It is known that the synthetic hormone can produce hypertension in these patients, and Perera, Loeb et al (32) also observed a similar effect in three patients without adrenal disease. In an Addisonian patient who had had hypertension prior to the onset of hypoadrenalism, Perera noted (33) that blood pressure remained at hypertensive levels when DCA was given but dropped to normal when salt alone was used. In the present series, the development of hypertension appeared to vary with the individual patient rather than with the amount of hormone given, a phenomenon also shown in the data of Perera et al (32). Small amounts of DCA were capable of producing hypertension in some Addisonian patients, but in others the administration of large amounts of DCA over long periods of time did not result in an elevation of the blood pressure above the normal levels obtained with the use of sodium chloride alone. Recently, Knowlton, Loeb, Stoerk and Seegal observed that sodium chloride potentiated the hypertensive (and other toxic) effects of DCA on normal rats and rats made nephritic with a cytotoxic serum (34).

Further light is shed on the mechanism underlying the hypotension by the work of Ghrist (31), Rowntree and Snell (23), Swingle (35), Loeb (29), Talbott (36), and their co-workers. Ghrist directed attention to the lack of vasomotor tonus in untreated Addisonian patients, a defect which does not occur in essential hypotension according to Rowntree and Snell. Working with animals, Swingle et al obtained evidence suggesting that the rise in blood pressure in dogs treated with DCA is due to an increase in arteriolar and capillary tone. Loeb would ascribe the increase in blood pressure, since it may result from the use of sodium chloride alone, to an ion effect on the vessels rather than to direct hormone action. However, these deductions are not in accord with other observations. For example, striking improvement may be seen in adrenalectomized animals following a large dose of cortical extract and before any demonstrable change occurs in electrolyte or water content of the blood (29). Talbott and his co-workers have recently obtained evidence in Addisonian patients of a persistence of diminished efferent glomerular arteriolar tone even after many months' treatment with DCA. Vasopressor drugs have no lasting effect on the hypotension and do not correct the postular component. Thus it appears that the hypotension is manifested by a lack of vasomotor tonus secondary to the absence not only of DCA but probably also other cortical hormones.

3 *Crisis* The most serious and striking cardiocirculatory abnormality which occurs in this disease is the vasomotor circulatory collapse known as the Addisonian crisis. In the present series it occurred at least once in forty-five of the fifty

patients, and in twenty instances it was the cause of the patient's first hospitalization. Clinically crisis closely resembles traumatic shock except that it is not necessarily acute in onset. It usually begins with vomiting which persists and is soon accompanied by progressive weakness followed by apathy and drowsiness. These symptoms may develop in the course of a few hours to a few days. Physical examination reveals a rapid thready pulse, a subnormal blood pressure, soft eyeballs and other evidence of dehydration and shock. Fever is frequently present, but subnormal temperature may also be encountered. Infrequently the onset is very sudden, all of the manifestations appearing abruptly. If untreated the vomiting becomes protracted and the weakness profound, the blood pressure continues to fall, the patient develops marked signs of delirium, lapses into coma and dies.

a *Precipitating factors* Crisis may ensue without a demonstrable precipitating cause. However, it has long been known that patients with Addison's disease are extremely susceptible to infection (37), trauma, operative procedures, and excessive exertion (19). A mild upper respiratory infection may precipitate a fatal crisis. In the present series, thirty-three patients suffered at least one crisis following a respiratory infection. High fever may be noted under such circumstances, even when the infection is mild. Hyperpyrexia may occur without demonstrable infection (38). Minor operative procedures, such as dental extraction, were formerly very much feared because they often precipitated a fatal crisis. Despite the advancement in therapy, major surgical intervention is still poorly tolerated by these patients, death often ensuing from crisis. However, cases have been reported in which successful major operations were performed (39).

b *Pathological physiology* The outstanding manifestations of crisis are comparable to those of traumatic shock. In both conditions the volume of circulating fluid and the blood pressure are reduced, the pulse rate is increased, the concentration and viscosity of the blood, the blood urea nitrogen, and the blood non-protein nitrogen content are all increased (40). However, the Addisonian crisis is usually produced by a lack of cortical hormone. Secondary to this deficiency is a loss of electrolyte and water through the urinary and gastrointestinal tracts which leads to a reduction in the circulating volume of fluid (8, 41, 42). Patients suffering from crisis do not respond to treatment which restores the volume of circulating fluid unless adequate amounts of sodium are given, alone or in conjunction with DCA or cortical extract.

Experimental work provides additional evidence concerning the intimate relationship between crisis and adrenocortical deficiency. A large dose of cortical extract may provide striking improvement before any demonstrable change in electrolyte or water metabolism has occurred (29). Certain types of shock in the adrenalectomized animal, such as those due to stress procedures, are influenced favorably only by treatment with carbohydrate-active cortical hormones and not at all by DCA (43) (44). Other types respond to DCA distinctly better than to the carbohydrate-active corticosterones, but this response depends on previous treatment with extracts containing small amounts of the carbohydrate-active

hormones (45). It is significant that cortical hormones are ineffective in the treatment and prevention of shock in the intact animal (46, 47). Thus, crisis probably reflects the manifold effects of a deficiency of all active cortical hormones.

4 *Electrocardiographic findings* Abnormal electrocardiographic tracings are frequent, especially after treatment with DCA (48, 49, 39, 22). The abnormalities observed are: low voltage of the QRS complexes, prolonged PR and QT intervals, low or inverted T waves, slight depression of RT segments, absent or small R4 waves, sinus bradycardia. Such changes were found in twenty-four of thirty patients in the present series. However, in five patients there was post-mortem evidence of organic heart disease unrelated to the Addison's disease. Normal tracings were obtained in six patients prior to treatment. Prolonged treatment with DCA and salt resulted in the development of ECG aberrations in these patients, and progressive changes were noted in 50% of all patients receiving this therapy. One patient, whose electrocardiogram before treatment was normal, developed sinus bradycardia, slurring of the QRS complexes and T wave inversions when treated with an excessive amount of DCA. Withdrawal of the hormone resulted in a return of the tracing to normal, but after treatment with maintenance doses of DCA and sodium chloride for two years RT depressions and T wave changes appeared.

The presence of abnormalities in the electrocardiogram prior to any treatment suggests that the changes may be related to the adrenocortical insufficiency. A relation between electrocardiographic changes in adrenalectomized dogs and renal retention of potassium has been suggested (50, 51). Other factors must also be considered. These include the effect on the myocardium of the lowered blood sodium and chloride values, the decreased blood volume, the general malnutrition, the disturbances in carbohydrate and protein metabolism.

The development or progression of electrocardiographic abnormalities during treatment with DCA may be related to several factors. Hypopotassemia resulting from the treatment may be responsible. The occurrence of electrocardiographic changes in association with spontaneous hypopotassemia is known (52, 53). The electrocardiographic changes may be due to the presence of myocardial lesions. In the present series focal myocardial necrosis was noted in seven of eight patients who had been treated with DCA. These lesions were not present in any of the eleven patients who died before DCA was in use. The lesions observed were similar to those recently reported in a case of Addison's disease (54) and to the focal myocardial necroses which can be produced in animals by potassium deprivation or by administering excessive amounts of DCA (55, 56, 57). Other contributing factors include the increase in the blood volume, the hypertension and the cardiac enlargement, all of which can be produced by the synthetic hormone. The myocardium may also be affected by the deficiency of the cortical factors concerned with carbohydrate and protein metabolism uncorrected by treatment with DCA and salt.

5. *Cardio-roentgenographic findings* A small⁵ heart is revealed by x-ray ex-

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amination in untreated cases of Addison's disease (58) Treatment with DCA and sodium salts results in an increase in the heart size, and recently x-ray determination of the cardiac dimensions has been recommended as a means of gauging the effect of such treatment (59)

F Disturbance in renal function, electrolytic and water metabolism

1 *Impaired renal concentration* During crisis, changes indicative of marked impairment of kidney function are readily demonstrated A marked increase in the blood non-protein nitrogen often occurs, and there may be an appreciable elevation of blood sulfate, creatinine, uric acid and phosphate levels The most significant findings, those of excessive loss in the urine of sodium, chloride and water, are almost always encountered in adrenocortical insufficiency A negative water balance is revealed by charting the fluid intake and output, and routine urinalysis often discloses evidence of impaired renal concentrating power In the present series, the specific gravity of the urine was usually less than 1 020 and did not exceed 1 022 in any of the patients who exhibited clinical evidence of adrenal cortical insufficiency or were in crisis Talbott and his co-workers (36) also noted a maximum specific gravity of 1 024 or less in ten Addisonian patients who were studied carefully while receiving adequate salt or hormone therapy Fishberg (60) states that if kidney function is unimpaired the specific gravity of the urine will exceed 1 022 and often go as high as 1 032 during a concentration test Impairment of urinary concentrating power is often present even in the dehydration of crisis, attributable to the antecedent negative salt balance Greenhow, in the Croonian Lectures of 1875, noted that the urine was generally of low specific gravity (61) Impairment in renal concentrating power was emphasized by Rosenow (62), and Rowntree and Snell (23) Rowntree (63), earlier reported decreased excretion of phenolsulphonphthalein in ten of twelve patients who were examined during an intercritical period

2 *Urinary clearance studies* More precise studies were made possible by the development of methods measuring the urinary clearance using creatinine, inulin, diodrast and glucose Margitay-Becht and Gomori (64) applied the creatinine clearance test of Rehberg (65) to three Addisonian patients before and after injections of adrenal cortical extract Prior to treatment there was marked reduction in the clearance values Following the parenteral administration of cortical extract a significant increase occurred in the amount of blood cleared per minute, but restoration to normal of tubular function and glomerular filtration took place in only one of the three patients

Talbott and his co-workers (36) recently made a very thorough study of renal function in ten patients suffering from Addison's disease In addition to the commonly used methods (determination of serum non-protein nitrogen content, urine concentration test, phenolsulphonphthalein excretion, intravenous pyelography), they employed newer clearance tests for inulin, creatinine, diodrast, glucose, sodium and potassium (66, 67) These procedures were carried out while the patients were under treatment with sodium chloride, later they were repeated when DCA was added Two of their patients were also given

adrenal cortical extract In contrast to the paucity of findings revealed by the commonly used methods, the clearance tests disclosed evidence in all of the patients of consistent impairment of all the aspects of renal function which were measured The rate of formation of glomerular filtrate and of tubular reabsorptive capacity for glucose were most affected The rate of plasma flow in the kidney was affected less and the maximum tubular capacity for excreting diodrast was affected least The filtration fraction was depressed below normal The administration of desoxycorticosterone acetate alone or in conjunction with cortical extract corrected these deficiencies only partly and temporarily It is of interest that Talbott et al. (36) were unable to demonstrate any significant alteration in the tubular absorption of water or any dissipation of sodium in the urine either before or during treatment with DCA However, as these authors point out, their findings are not in keeping with observations on adrenalectomized animals, and they emphasize that the patients were under treatment and not suffering from adrenal cortical insufficiency Following the injection of DCA, an increased renal clearance of potassium was noted. This was due mainly to an increase in glomerular filtration

Results similar in many respects to those of Talbott et al were obtained in the very recent studies of kidney function carried out on a similarly treated group of patients with adrenal insufficiency by Waterhouse and Keutmann who employed mannitol and para-amino-hippuric acid clearance tests (68, 69, 70). The distinctive features of the derangement of renal function found in these studies (71) were (a) permanent decrease of renal blood flow and glomerular filtration rate in all patients and (b) reduction of the maximum capacity of the tubules to excrete para-amino-hippuric acid in all female patients The latter aspect of renal function was normal in all the males except two who had hypertension Treatment of several female patients with testosterone propionate and adrenal cortical extract in addition to salt and DCA was without significant effect Waterhouse and Keutmann stressed the consistent finding of decrease of renal blood flow and glomerular filtration rate regardless of the presence or absence of impairment of the tubular cells to excrete para-amino-hippuric acid Then data led them to postulate a reduction in the effective vascular bed in the kidneys with resulting decrease of renal plasma flow and concomitant reduction in the rate of glomerular filtration

An additional point of interest was the possible use of the filtration fraction in determining the underlying pathology in adrenal cortical insufficiency Based on their own findings and on the similar results of Talbott et al, Waterhouse and Keutmann pointed out that the patient with Addison's disease prior to specific treatment apparently will show a low filtration fraction whereas the untreated patient with panhypopituitarism may be expected to have a high filtration fraction

To summarize, patients having Addison's disease present evidence of impaired renal function Marked changes are encountered during crisis More precise methods reveal unequivocal evidence of impairment during the intercritical periods

3 *Basis of renal dysfunction* It appears unlikely that the renal dysfunction has an anatomical basis Talbott and his associates concluded from their own findings and a review of the literature that "structural changes (in the kidney) are observed infrequently in Addison's disease and cannot be held responsible for the functional impairment" (36) This view is also borne out by the pathological findings in the present series Conspicuous round cell infiltration, usually in the cortex, was found in the kidneys in eight out of twenty-one cases In four of these cases there was focal cortical atrophy, and in a fifth case subcapsular atrophy was present

The experimental work of Harrison and Darrow (72) appears to have considerable bearing on the pathogenesis of the renal dysfunction Following adrenalectomy in dogs, Harrison and Darrow found an inability of the renal tubular cells to reabsorb sodium in a normal manner from the glomerular filtrate at a time when the concentration of sodium in the plasma was low There was also inability to excrete potassium and phosphate normally when these ions were present in high concentration in the blood plasma Secondary to the loss of sodium and chloride, there occurred a diminished rate of glomerular filtration These changes in the adrenalectomized dog could be reversed in part by the administration of sodium salts and completely reversed by the injection of adrenal cortical extract

4 *Loss of sodium and water in the urine and from extracellular fluid* A special interrelation between the renal tubules and the adrenal cortex may be responsible for the diminished ability of the former structure to reabsorb sodium in a normal manner in adrenocortical insufficiency However, the tubular dysfunction may be part of a generalized inability of all the body cells to retain salt In any event the chief loss of salt and water is through the urine, each milliequivalent of sodium being excreted with 6.5 c.c. of water (73)

A corresponding change occurs in the composition of the extracellular fluid In order to equalize the osmotic pressure between the sodium-depleted, hypotonic, extracellular fluid and the cells which it bathes, water probably leaves the extracellular fluid and enters the cells, (Gamble) (74) As a result, the loss of sodium through the urine is accompanied by a twofold loss of water from the extracellular fluid, a loss through the renal tubule and a loss into the cells

5 *Sodium loss through intestines* Loss of sodium and water also takes place through the intestinal tract This results not only from vomiting and diarrhea, but also from impaired absorption of electrolyte through the lumen of the intestine (75) Such impairment occurs in adrenalectomized animals and can be corrected by injections of cortical extract (76) Gastrointestinal disorders augment but are not primarily responsible for the loss of electrolyte and water inasmuch as significant dehydration precedes the onset of the vomiting and diarrhea in the experimental animal (8) A similar sequence of events is commonly observed in Addisonian patients

6 *Potassium retention* In adrenal cortical destruction the blood plasma potassium level is elevated, in sharp contrast to the reduction in plasma sodium and chloride There is a similar inverse relationship in the urinary excretion of

potassium as compared to that of sodium and chloride. An increase of the potassium content of the intercellular fluid and of the cells accompanies the increased concentration of this ion in the plasma, probably because of the failure of the renal tubule to excrete adequate amounts of potassium ion (72). However, it has been suggested by Marenzi (77) that a disturbance in the potassium-binding ability of the cells may also play a role in producing the increased concentration of this ion in the blood plasma. Marenzi found that adrenalectomized animals fixed injected potassium in the tissues less readily than did the controls.

7 *Effects of DCA on electrolyte and water metabolism* DCA has a pronounced effect on salt and water metabolism, greater than that of any other cortical hormone available. It reduces the loss of sodium excreted by the kidney (78, 79) thus increasing the concentration of sodium, chloride and water in the blood plasma and extracellular fluid. It may also have a favorable influence on the sodium metabolism in adrenalectomized animals and Addisonian patients by influencing the absorption of this ion from the intestinal tract (75) and by abolishing vomiting and diarrhea. Desoxycorticosterone has a marked effect on potassium metabolism. It increases the excretion of potassium in the urine (80) and regulates the passage of this ion into and out of cells (81). The administration of desoxycorticosterone will also prevent the increase in intracellular potassium (82). These effects are not limited to Addisonian patients or adrenalectomized animals, but take place in normal subjects and animals. The inability of this hormone to restore renal function completely to normal in patients having Addison's disease (36) may indicate that DCA is not the only adrenal cortical hormone which influences renal function. DCA apparently has no direct action on carbohydrate or protein metabolism.

8 *Sodium chloride excreting hormone* Thorn and his co-workers noted that 11-desoxy-17-hydroxycorticosterone manifested a less marked sodium and chloride retaining effect than desoxycorticosterone (83). This led these authors to examine the effect of the addition of an hydroxyl group on C 17 of corticosterone. The compound which resulted, 17-hydroxycorticosterone, had not only a less marked sodium and chloride retaining effect than the original compound, but actually facilitated the excretion of these ions (84). This work supports the view that the adrenal cortical regulation of salt and water metabolism depends not only on the participation of a salt-retaining but also a salt-excreting hormone (85). In this concept it was also postulated that the human adrenal cortex besides manufacturing these hormones could also under certain conditions convert one into the other.

G Disturbances in carbohydrate and protein metabolism

1 *Hypoglycemic symptoms.* The symptoms and signs discussed thus far were all mentioned in Addison's original description of the disease. He could not have known that some symptoms were due to hypoglycemia. Subnormal blood glucose values were first noted in adrenalectomized animals and in Addisonian patients by Porges (86) fifty years after the disease had first been described. The discovery of insulin, some seventy years after Addison's paper revealed that hypoglycemia can produce weakness, dizziness, headache, sweating, fainting, shock,

peculiar types of behavior and certain neurological aberrations (87) Such manifestations are often difficult to differentiate from those due to sodium depletion, unless relief is obtained following the ingestion of glucose Symptoms of hypoglycemia occurred at one time or another in 60% of the patients in the present series

2 *Symptomless hypoglycemia* Subnormal or low normal fasting blood sugar values were obtained in 80% of the patients considered, but about half of this number had no clinical manifestations of hypoglycemia at the time the blood was drawn However, as observed by other authors (23, 88) these patients showed a marked tendency to develop striking hypoglycemia This occurred especially under the following circumstances fasting for twenty-four or more hours, following the oral or intravenous administration of large amounts of glucose, during fever or infections, when undergoing operative procedures regardless of the type of anesthesia used Thorn et al (88) noted that hypoglycemia can also result if the patients are fed a diet which is high in fat and low in carbohydrate content These authors emphasized that the threshold for hypoglycemic symptoms is decreased in Addisonian patients

3 *Other manifestations of disturbance in carbohydrate metabolism* Patients suffering from Addison's disease frequently have a low normal basal metabolic rate, a decreased glycemic response to epinephrine, a sensitivity to insulin, a flat type of glucose tolerance curve following oral administration of sugar, and, as shown by Thorn et al (88), an absence of rebound in the blood glucose curve following intravenous administration of sugar, a high standard respiratory quotient and an increase over normal in respiratory quotient following glucose administration In the present series 13 out of 18 patients exhibited a flat oral glucose tolerance curve following administration of 175 grams/kilo of glucose, and a basal metabolic rate of less than minus 10% was found in 13 out of 20 patients

4 *Nature of the disturbance in carbohydrate metabolism* Animal experimental work provides direct evidence of a relationship between the adrenal cortex and carbohydrate metabolism, as claimed by earlier workers (86, 89, 90, 91, 92) Britton and Silvette, beginning in 1931, demonstrated that adrenalectomy was followed by a disturbance in carbohydrate metabolism, manifested by hypoglycemia and a depletion of hepatic and muscle glycogen and prevented or corrected by adrenocortical extract (93, 94) As a result of their fundamental work and the subsequent contributions of other authors, it is now known that the following phases of carbohydrate metabolism may be disturbed in adrenocortical insufficiency

a *Faulty intake and absorption of carbohydrate* There is a reduced intake of all foods, including carbohydrates, as a result of the anorexia, in Addisonian patients and bilaterally adrenalectomized animals The rate of absorption of glucose from the small bowel is diminished (7) Fasting results in hypoglycemia and in the animals is accompanied by a marked fall in hepatic glycogen (93, 94) Treatment with sodium salts and adequate feeding can prevent or correct these manifestations in animals and in some patients (95, 96)

Impaired intestinal absorption of glucose in Addisonian patients was demon-

strated by Thorn et al. who obtained flat oral, but normal intravenous glucose tolerance curves (88). Following prolonged treatment with DCA and salt, the oral glucose tolerance curve became more normal, reflecting an improvement in the intestinal absorption of glucose. Similar observations were made in the present series. However, the improvement was apparent only if capillary blood was examined; venous blood determinations yielded flat curves persistently (97, 98), indicating that DCA and salt therapy influenced the intake and absorption of carbohydrate, but apparently did not affect the increased rate of glucose utilization in the tissues. The latter, accepted as an alteration characteristic of adrenocortical insufficiency, will be discussed below.

b. *Disturbance in glycogenesis and glycogenolysis*. Britton and Silvette were the first to demonstrate that the administration of cortical extract could prevent or correct the hypoglycemia and glycogen depletion of adrenalectomized animals, a rise in the blood sugar level and an increase of the glycogen stores was also observed in normal animals. Recently Britton and Corey (99) demonstrated that perfusion of the liver of an adrenalectomized rat with a Ringer gum-glucose solution did not result in significant glycogen storage (even if insulin were given) unless cortical extract was added to the perfusing medium. On the other hand, Seckel provided evidence that cortical extract decreases the rate at which hepatic glycogen is converted to glucose (100).

c. *Faulty formation of carbohydrate*. Long, Katzin and Fry noted that the augmented blood glucose content and the increased hepatic glycogen content resulting from cortical extract was accompanied by an increase in urinary nitrogen excretion (95). The ratio of the extra glycogen formed to the extra nitrogen excreted indicated that the increased glycogen could be entirely accounted for by conversion from endogenous protein stores. This work is in accord with the earlier observations of Evans (101) who noted a reduction in the nitrogen excretion of fasting adrenalectomized animals, and of Long and Lukens (102) who pointed out that the alleviation of pancreatic diabetes by adrenalectomy was attended not only by a decrease in glycosuria but also in urinary nitrogen. The administration of cortical extract to the pancreatectomized adrenalectomized animals resulted in an increase in the excretion of both glucose and nitrogen. Parallel findings were obtained in phlorhizin treated adrenalectomized animals. Normal animals treated with phlorhizin excreted several times as much glucose and nitrogen as did similarly treated adrenalectomized animals (101). However, when the latter were also treated with cortical extract or carbohydrate-active cortical hormones there resulted a loss in body weight accompanied by increased glycosuria and increased urinary nitrogen excretion (103).

That the adrenal cortex exerts an influence on intermediate protein and carbohydrate metabolism is also substantiated by other observations. Russell and Wilhelm (104) recently corroborated and extended the work of Jimenez-Diaz (105) which showed that kidney slices from adrenalectomized animals did not deaminate amino acids at a normal rate. Russell and Wilhelm also showed that such tissue oxidized certain keto acids and succinic acid at rates less than normal. Samuels et al. (106) noted that the feeding of alanine resulted in less

glycogen storage in adrenalectomized than in normal rats. Lewis and his co-workers (107) observed that the formation of glucose from lactic and pyruvic acids, as well as from alanine, is subnormal in the adrenalectomized phlorrhizimized rat. The formation of glycogen from lactic acid was found to be retarded (108) in the liver of adrenalectomized rats. Pyruvate and glycogenic amino acids also do not appear to undergo glycogenesis at a normal rate in the liver tissue of the adrenalectomized animal (88). However, the addition of adrenal cortical extracts to liver slices from rats resulted in a conversion of lactic and pyruvic acids to carbohydrate at a rate greater than normal (109). While further confirmation is necessary, there seems to be little doubt that the formation of carbohydrate from the intermediate products of protein and carbohydrate catabolism is impaired when adrenal cortical hormone is lacking.

Similar views have been expressed on the basis of observations in Addisonian patients. Thorn et al. (88) noted a favorable influence on the carbohydrate metabolism following the administration of adrenal cortical extract, 17-hydroxy-11-dehydrocorticosterone, or corticosterone. Elevation of the blood glucose level following an intravenous glucose test was accompanied by an increase in the urinary nitrogen excreted and a decrease in the respiratory quotient. Their data suggested that adrenal cortical hormone increases the ability of the organism to form glucose and glycogen from intermediary products of both carbohydrate and protein metabolism, and in this manner regulates the utilization of carbohydrate.

d Impaired utilization. The rapid rate at which hepatic glycogen diminishes in a fasted adrenalectomized animal cannot be explained by faulty protein catabolism alone. This indicates that the tissues are oxidizing carbohydrate at an abnormally rapid rate. In keeping with this view, Ingle and Thorn (110) noted that adrenalectomy corrected the glycosuria of partially depancreatized diabetic rats but did not decrease the excretion of nitrogen. Evans (101) also found that adrenalectomy resulted in an increased tendency of the glucose-fed animal to oxidize carbohydrate, and a decreased ability to store it as glycogen. The converse, an increase in the glycogen stores and a decrease in the amount used in the tissues, was obtained in similarly fed adrenalectomized animals by Russell (111) following injection with adrenal cortical extract. Long, Katzin and Fry (95) had previously observed that the injection of cortical extract in glucose fed normal rats resulted in a depression of the respiratory quotient indicating decreased carbohydrate oxidation (as compared to glucose-fed normal rats not so injected).

A similar depression of the respiratory quotient in Addisonian patients (88) suggests that the cortical hormones inhibit the utilization of carbohydrate in these patients. However, MacBryde and de la Balze (112) recently observed, while treating Addisonian patients with the "highly carbohydrate-active" pork extract, that the glucose content of the venous blood was decreased despite the fact that simultaneously there occurred a significant increase in the capillary blood-glucose content. The increase in the arteriovenous glucose difference was interpreted as indicating that increased and not decreased tissue oxidation of the

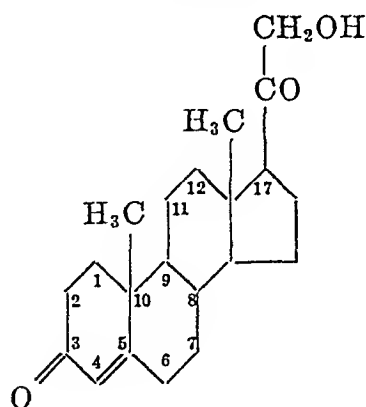
sugar had resulted from the use of the extract. Respiratory quotients were not reported. The possibility that the decrease in the venous blood-glucose is due to increased carbohydrate storage in the tissues was not ruled out. It will be recalled that a similar arteriovenous glucose difference was noted in patients in the present series who received prolonged treatment with desoxycorticosterone acetate alone. The evidence favors increased tissue oxidation of carbohydrate when the adrenal cortical hormones are lacking.

e *Insulin-corticosterone antagonism*. The antagonistic effects of the carbohydrate-active corticosterones to insulin, demonstrated by Jensen and Grattan (113) help to explain the reduction in tissue oxidation of carbohydrate produced by the cortical hormones. These authors were able to protect mice against insulin hypoglycemia by injecting cortical extract or corticosterone acetate, thus demonstrating that these substances inhibit the action of insulin. In consonance with these findings is the very recent work of Cori and his collaborators (114, 115) which demonstrates that adrenocortical extract enhances the inhibiting effect of anterior pituitary extract on hexokinase, whereas insulin counteracts this inhibition of the enzyme.

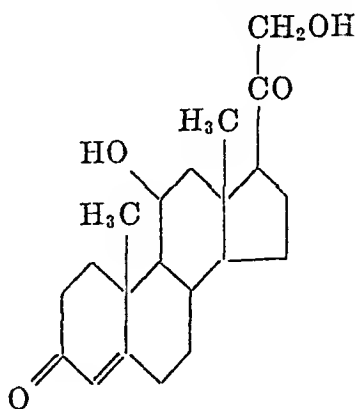
f *Summary*. Adrenocortical insufficiency leads to a profound disturbance in several important phases of carbohydrate metabolism. This includes not only a reduction in the intake and the intestinal absorption of carbohydrate but also involves its storage, formation and utilization.

5 *The carbohydrate-active cortical hormones*. A thorough presentation of this subject was recently published by Ingle (116). The six biologically active hormones may be divided into two groups—the desoxycorticosterones and the corticosterones. The latter possess an hydroxyl group at C 11 as shown.

Desoxycorticosterone



Corticosterone



There is a marked difference in the action of the two groups. 11-Desoxycorticosterone is concerned chiefly with electrolyte and water metabolism, while the oxygenated C 11 steroids of the corticosterone type exert a marked effect on carbohydrate and protein metabolism. The effects may be elicited not only in the absence of the adrenal cortex but also when this organ is intact.

H Manifestations of other endocrine gland dysfunction

Adrenal cortical destruction is associated with anatomical changes and dysfunction of other endocrine glands. Observations on experimental animals relate the adrenal to the pituitary (117), the thyroid (118), the gonads (119), the pancreas (102), the thymus (120, 121), and perhaps the parathyroid (122, 123). This relationship is also manifest in patients suffering from Addison's disease.

1 *Pituitary gland a Hypopituitarism* Symptoms characteristic of adrenal cortical destruction, such as asthenia, loss of flesh, low blood pressure and hypoglycemia are also present in patients afflicted with fibrosis of the anterior lobe of the pituitary gland as seen in Simmonds' disease (124). This suggests that the pituitary gland may also be involved in Addison's disease. The histologic evidence of such involvement consists of a striking reduction in the number of basophilic cells in the anterior pituitary lobe (125, 126), in some instances fibrosis of this portion of the hypophysis is present (127, 128). The anterior pituitary lobe, examined in seven cases in the present series, showed a marked reduction in the number of basophilic cells in five cases, four of which showed additional significant alteration. A marked reduction in the number of eosinophilic cells and widespread fibrosis were each respectively present in two cases.

It is entirely probable that the morphologic changes in the anterior pituitary lobe may be responsible for some of the clinical manifestations of Addison's disease. Kraus (125), and Crooke and Russell (126), who noted the reduction in the number of basophilic cells, pointed out that this change might play a role in the production of the hypoglycemia and the hypotension in Addisonian patients, since hyperpituitarism due to basophilic adenomata of the pituitary gland is accompanied by hyperglycemia and hypertension. These and such other manifestations of pituitary dysfunction as sterility, may be due directly to involvement of the anterior lobe of the hypophysis and indirectly to dysfunction of other endocrine glands.

b *Evidence of primary adrenocortical involvement* The alterations in the pituitary gland noted above occur in cases of adrenocortical destruction due either to idiopathic atrophy or to tuberculous destruction. This is strong evidence that the pituitary changes are not the precursors of, but rather the sequel to adrenal cortical destruction. Further proof that the changes in the adrenal cortex in Addison's disease including those due to non-tuberculous idiopathic atrophy are of a primary nature is provided by the histopathologic studies of Crooke and Russell (126). These authors examined the histologic structure of the adrenal gland in five cases in which there was adrenal atrophy secondary to destruction of the anterior lobe of the pituitary gland. They found that the changes in the adrenal gland were those of simple atrophy not associated with cellular infiltration or fibrosis even though the cortex was reduced in depth and the cortical cells were reduced in number and size. The appearance differed markedly from that seen in the idiopathic cellular atrophy encountered in Addison's disease.

2. *Thyroid gland* Atrophy of the thyroid gland occurs in Addison's disease. The incidence of thyroid changes is so high in association with cytotoxic adrenocortical atrophy that the existence of a bi-glandular disease, thyro-suprarenal disease (M B Schmidt), has been suggested (129). However, similar changes in the thyroid occur in Addison's disease of tuberculous etiology, and in practically all cases of adrenocortical destruction in which the thyroid is involved other endocrine glands are also affected. In the present series the thyroid gland showed significant changes in twelve of sixteen cases. Marked replacement of the parenchyma by extensive lymphocytic proliferation occurred in seven cases, in three of which conspicuous fibrosis was also present. The lymphocytic proliferation replaced a considerable amount of glandular parenchyma producing a virtual atrophy.

The thyroid atrophy may be so extensive in some cases of Addison's disease that symptoms of hypothyroidism should have resulted. Mild symptoms may easily be masked by those of adrenocortical origin. However, classical myxedema has been encountered by Rowntree and Snell (23). A somewhat similar case is described by Marsh (130), and Brenner (26) mentions symptoms of myxedema in several patients.

a. *Hypothyroidism* Several patients in the present series had symptoms of hypothyroidism. One patient had classical myxedema which became manifest during treatment for Addison's disease. The basal metabolic rate dropped to minus 30 per cent and the blood cholesterol content rose to 450 mgm. per cent. Improvement was noted when small amounts of thyroid extract were added to the cortical hormone and salt therapy. In a second case in which the basal metabolic rate gradually decreased within a six year period from minus 10 to minus 30 per cent clinical manifestations of hypothyroidism were present, but thyroid extract although well tolerated was without significant effect. A third patient presenting definite clinical manifestations of hypothyroidism had enlargement of the thyroid gland as seen in diffuse colloid goiter.

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developed Addison's disease. The administration of desoxycorticosterone had no effect on the lowered blood sugar, but following the use of cortical extract the hyperglycemia recurred. Similar observations were made by Bloomfield (144).

c *Insulin sensitivity* Sensitivity to insulin appears to be as common in Addison's disease combined with diabetes mellitus as in the former alone. The presence of hyperglycemia does not correct this sensitivity. Rogoff (143) discusses a case of Addison's disease which developed in a patient with diabetes mellitus following bilateral adrenal denervation carried out by a surgeon as "harmless" procedure in an attempt to benefit the diabetes. This apparently resulted in occlusion of blood vessels and degeneration of the adrenal cortex. The fasting blood sugar values became lower, the patient developed sensitivity to insulin and died in hypoglycemia.

d *Relationship of the diabetes to the Addison's disease* The diabetes is reported to have appeared after the Addison's disease⁶ in only four cases (146, 147, 148, 149), but the insidious onset characteristic of both diseases makes it difficult to determine the actual sequence. In contrast to the inconstant presence of macroscopic and microscopic changes in the pancreas in uncomplicated diabetes mellitus (157), marked changes in the pancreas have been reported in the cases mentioned. Atrophy of the pancreas was present in eight of the ten cases in which that organ was examined histologically. Evidence of pancreatic atrophy is recorded in at least seven cases of Addison's disease in which diabetes was not noted clinically (125, 126, 127). Five were of tuberculous etiology, the weight of the pancreas in two of these cases was 35.2 and 25 grams respectively.

It is of interest that in twelve of the fourteen autopsied cases of combined Addison's disease and diabetes mellitus, idiopathic atrophy of the adrenal glands was found, in only two cases was the cortex destroyed by tuberculosis. This incidence represents an inversion of the ratio of these etiologic factors as causes of Addison's disease. Atrophic changes in the pituitary, thyroid and gonads also occur more frequently in association with idiopathic adrenal atrophy than with cortical destruction due to tuberculosis. The possibility that the pancreatic involvement is related to pituitary dysfunction is suggested by the occurrence of pancreatic atrophy in Simmond's disease (124). The frequency of thyroid changes and the fact that a thyroid-pancreatic relationship appears to exist (158) suggest that alterations in the thyroid gland may contribute to the pancreatic changes. On the other hand, Levy-Simpson has implied that the atrophic process in the adrenals and the pancreas may be caused by the same factor or toxin (141).

5. *Thymus gland and lymph nodes.* Addison directed attention to an enlargement of the lymph glands in one of his cases. Star in 1895 noted enlargement of the thymus (159), and later other authors (160, 161, 126) commented on the occurrence of generalized lymphatic hyperplasia. Hyperplasia of the thymus gland and of the lymphatic tissue throughout the body was observed frequently

⁶ The first symptoms in one of the patients in this series were those of cortical insufficiency, but both conditions were found at the first examination.

in the present series. The similarity of this hyperplasia with the so-called status thymico-lymphaticus has been stressed (162, 163) and it has been suggested that sudden death in Addison's disease may be explained in this way. Jaffe was able to produce hyperplasia of the thymus by adrenalectomizing immature rats and thymus gland regeneration by subjecting mature rats to the same operation (120, 121). Several authors including Hammar (164) doubted that genuine thymus hyperplasia occurs in Addison's disease. However, the frequent occurrence of lymphatic tissue hyperplasia in Addison's disease is now considered significant. The more recent work of Moon (165), Selye (166), Ingle (167), Wells and Kendall (168), and of White and Dougherty (169) establishes the existence of an adrenocortical-lymphatic tissue relationship which is under the influence of the pituitary adrenocorticotrophic hormone. The alterations in the lymphatic organs in Addison's disease may contribute to the clinical picture.

6 *Parathyroids*. Hypercalcemia occurs constantly in adrenalectomized animals and in Addisonian patients. There is no direct evidence that the parathyroid and adrenal glands are interrelated.

7 *Panhypocorticalism*. Addison's disease with multiglandular insufficiency.

Several patients in the present series showed the clinical picture of multiglandular insufficiency and striking confirmation of this was found at autopsy. These patients all had the classical manifestations of Addison's disease. However, they were less robust and less energetic, and despite therapy their asthenia and anorexia persisted with continuous loss of flesh. Moreover, hypoglycemia, lowering of the basal metabolic rate, loss of libido, amenorrhea, impotence, sterility and loss of body hair was more frequent and severe in these patients. A secondary anemia which responded poorly to iron therapy was observed frequently in association with hypoproteinemia. These patients also exhibited a marked tendency to edema while receiving DCA and salt. The latter measures were not always effective in maintaining life without the addition of cortical extract, and restoration to useful activity was not accomplished in these patients despite all measures.

Multiglandular insufficiency occurs much more frequently in cytotoxic atrophy than in tuberculous destruction of the adrenal cortex. The longer the duration of the Addison's disease, the more distinct the multiglandular symptoms. Extreme degrees of adrenocortical destruction were encountered at autopsy. Thus, panhypocorticalism is not a clinical state apart from Addison's disease but an advanced stage in its development.

The occurrence in Addison's disease of a multiglandular syndrome points to the need of more complete replacement therapy in those patients who do not do well with the usual treatment. In addition to cortical extract, the judicious use of other glandular preparations may be indicated. The fact that panhypocorticalism occurs makes it necessary to consider the possibility in evaluating the metabolic data in Addisonian patients. It also emphasizes the caution which must be employed in comparing studies on short-lived adrenalectomized animals with those in patients suffering from Addison's disease.

I. Neuropsychiatric and neurologic symptoms

1. *Observations of early students of Addison's disease* Addison pointed out that it was not uncommon for the patient "to manifest indications of disturbed cerebral circulation," and emphasized that the patient was indisposed "to either bodily or mental exertion." The occurrence of delirium and convulsions was noted as a terminal manifestation in one of his cases, in another, numbness of the fingers was recorded. Samuel Wilks, who participated with Addison in the original work (170), in reporting on a series of twenty-five cases in 1862, called attention to "Special Nervous Symptoms" (171). Averbach (172) in a monograph on Addison's disease written in 1869 spoke of poverty of mental energy, a diminution of the intellect, loss of memory, of apathy and depression, and called attention to the occurrence of headache, insomnia, transitory delirium, mild psychoses, convulsions and epileptiform attacks. He noted that neuralgias, anaesthesias, and paralyses also occurred. All of these he attributed to inadequate nutrition. Neusser (173) in 1897 in his monograph, "The Diseases of the Adrenal Glands," divided the nervous symptoms into three groups. The first group, the "psychic sphere," included manifestations of impairment in intellect as well as those of psychotic behavior. The latter consisted of irrational speech, religious illusions, hallucinations, paranoia and maniacal behavior. Under "cerebral symptoms," his second group, he listed insomnia, headache, dizziness, tinnitus aurium, and a tendency to syncope. The third group, comprised symptoms of peripheral nerve involvement including parasthesias and neuralgias. There was mention of a patient who presented the clinical picture of spastic spinal paralysis.

2 *Clinical significance* The onset of mental signs in an Addisonian patient, noted in 70 per cent of the patients in this series, is of utmost clinical significance. It has been pointed out by Engel and Margolin (174) that changes in mood or behavior not infrequently are the earliest signs of impending collapse. In the present series, mental changes occurred in almost all patients prior to the onset of crisis. The appearance of cerebral symptoms during treatment of adrenal insufficiency is also of major importance. A comparison may be made to the development of similar symptoms in hepatitis presaging an acute yellow atrophy (Thanhauser) (175). The appearance of confusion, disorientation or irrational behavior in patients undergoing treatment indicates a grave prognosis, unless the symptoms are due to a readily reversible hypoglycemia. The early recognition of changes in the level of awareness is of great importance since treatment with DCA and salt may obscure other signs.

3 *Neuropsychiatric symptoms and the delirious state.* The neuropsychiatric symptoms of Addison's disease are manifestations of the delirious state not unlike those seen in other diseases. Romano and Engel (176), who have recently made very significant contributions to the study of cerebral metabolic disturbances, define delirium as "a more or less reversible psychotic episode appearing symptomatically during the course of an underlying physical or metabolic disorder." These authors consider the basic psychologic symptom of delirium to be a dis-

turbance in the level of consciousness, and point out that there is also a loss of ability to think in the abstract. They interpret the total behavior of the delirious patient as due to a release from higher cerebral function. The abnormalities in emotional behavior are viewed as due to a release of inhibiting or repressing factors which permit the expression of repressed emotions within the framework of the specific personality structure of the individual. The neurologic basis of the peculiar purposeless movements commonly seen in delirium is found in a release from cortical control and a return of motor behavior to a lower order of integration.

4 *Mild neuropsychiatric symptoms* Romano and Engel point out that lesser and more subtle manifestations of delirium occur much more frequently than marked changes. An analysis of the neuropsychiatric symptoms observed in the patients in the present series bears this out. Mild disturbances in the level of consciousness occurred most frequently. These consisted of dulling of the intellect, apathy, somnolence and also of insomnia and troublesome dreams. Next in frequency were mild degrees of confusion and disorientation. The significance of these changes is shown in the following observations. One patient under treatment for mild crisis due to an infection was reported by the nurse to be "talking peculiarly." She was found to be mildly confused and disoriented, but showed no other manifestations of cortical insufficiency. Blood drawn at this time revealed normal values for sodium, chloride and sugar. Shortly afterward the patient's temperature rose to 104° and she died several hours later despite intensive therapy. In a few instances there were recurrent disturbances in emotional behavior which reflected the specific personality structure of the patient. The family of one patient learned to recognize that whenever he became sullen, withdrawn and taciturn he was on the verge of crisis. Another patient who received daily injections of cortical extract became cross, surly and sometimes abusive if the extract was omitted for several days or if cortical insufficiency developed due to other reasons. However, over 70 per cent of the patients in the present series were placid and good natured often even during episodes of cortical insufficiency.

5 *Marked neuropsychiatric symptoms, psychoses* There were also more marked symptoms such as stupor, coma, increased motor activity including convulsive seizures, and various types of severe psychotic behavior. Among the latter were transitory psychoses observed frequently as subterminal occurrences. Three patients had clearly defined schizophrenic psychoses of longer duration, but none were violent. In two patients, the psychosis appeared after a febrile illness but at a time when the patients were in electrolyte balance. All were treated with DCA and salt supplemented with injections of cortical extract and Vitamin B. Improvement occurred in two of the patients after several weeks. The third patient improved for a short while but death ensued despite intensive therapy. In this patient chronic hypoglycemia was present for several years before the psychosis developed.

6 *Neurologic symptoms, spinal cord involvement* An increase in muscle tone is often present in adrenocortical insufficiency. This is sometimes associated

with muscular rigidity and pyramidal tract signs. Symptoms of peripheral nerve involvement including paresthesias, neuralgias and paralyses are encountered less frequently. One of the patients observed at the Hospital in 1925 had unequivocal evidence of Addison's disease associated with degenerative disease of the spinal cord allied to funicular myelitis, bilateral Babinski and Oppenheim signs were present. A second patient, a twenty-nine year old male, who has been under observation for ten years, has spinal cord disease manifested by a spastic broad-based gait and pyramidal tract signs in the lower extremities. Three similar cases have been reported by Neusser and Wiesel (173), and Snell and Rowntree (178). However, a definite relationship of the spinal cord involvement to adrenal gland destruction has not been demonstrated.

7 Basis a Hypoglycemia Hypoglycemia occurs frequently in Addison's disease. It is probable that many of the neuropsychiatric symptoms noted above are due to hypoglycemia or to the underlying disturbance in carbohydrate metabolism. Hypoglycemia may be manifested by general symptoms of central nervous system origin such as headache and fatigue, and by bulbopontine disturbances resulting in impaired vision and disorders of speech, corticospinal symptoms such as aphasia and convulsive movements, and symptoms of autonomic origin. Psychotic disturbances very similar to those observed in Addison's disease occur in hypoglycemia of any etiology.

b Hypotension The cerebral anoxia resulting from arterial and postural hypotension may also contribute to the production of cerebral symptoms.

c Cortical hormones 1 *Electroencephalographic studies* Engel and Margolin (174) studied the effects of disturbed carbohydrate metabolism on the electroencephalogram in eight patients with Addison's disease, seven of whom are included in the present series. These authors and also Hoffman, Lewis and Thorn (179) who examined twenty-five patients noted frequent electroencephalographic abnormalities in the resting pattern and an increased sensitivity to hyperventilation. Both groups of investigators reported that they were able to reduce this sensitivity by raising the blood sugar level. Engel and Margolin found that all of the changes were modified by factors which improved carbohydrate metabolism but Hoffman et al. observed no effect on the resting pattern following treatment with DCA, aqueous cortical extract or intravenous infusions of glucose. More recently, however, Engel and Romano noted that large quantities of aqueous adrenal extract alone or in conjunction with dextrose restored the electroencephalogram to normal. DCA and sodium chloride were less effective. The administration of crystalline fraction of the Vitamin B complex was found by them to be ineffective in correcting the electroencephalographic abnormalities (180).

2 *Clinical observations.* In several of the patients in the present series cortical extract was required for the complete reversal of neuropsychiatric symptoms, but the administration of DCA, salt and dextrose sufficed to achieve this result in others. The impression was obtained that improvement occurred more rapidly following the use of extract. The improvement of cerebral symptoms following the use of DCA may be due to the indirect effect of this hormone on carbohydrate

metabolism as well as to its action on electrolyte economy and on the blood pressure

d *Organic brain disease* A cerebral tuberculoma or tuberculous meningitis can produce neuropsychiatric symptoms similar to those mentioned. These conditions occur rarely in Addison's disease of tuberculous etiology

III LABORATORY FINDINGS

A *Blood electrolytes*

The concentration of sodium and chloride ion in the blood is frequently reduced and the potassium content often elevated in adrenocortical insufficiency, but this does not hold true for all Addisonian patients. Moreover, subnormal blood sodium and chloride values obtain in various other conditions, including severe infections, diabetic acidosis, uremia, severe diarrhea, and protracted vomiting whatever the cause (181). A marked decrease in the blood chloride content occurs in other diseases, notably pneumonia. As shown below, increased potassium content of the blood is encountered in conditions other than Addison's disease.

1 *Blood sodium and the sodium chloride deprivation test* The most reliable laboratory finding supporting a diagnosis of Addison's disease is a subnormal blood sodium value. With a single exception, all thirty-seven patients in the present series who were admitted to the Hospital after 1933 had a blood sodium content of less than 135 milli-equivalents per liter at one time or another during their illness. The values ranged from 114 to 130 milli-equivalents of sodium per liter. In eight instances this abnormality appeared only after the patient had been subjected to a sodium chloride deprivation regimen for several days (24). This test consists of limiting the total sodium intake per twenty-four hours to less than one gram while cortical hormone therapy is interrupted. There is but little danger in the use of this test if it is carried out in a hospital where the procedure can be interrupted as soon as signs of cortical insufficiency appear. In patients who had had no previous treatment a significant drop in blood sodium appeared as early as the third day of the test. Patients who had been treated, with supplementary salt and DCA in oil required longer periods, up to nine days of deprivation. A decrease in the blood sodium content to a subnormal value indicates the presence of Addison's disease unless other cause for loss of sodium is present.

a *Normal blood sodium in cortical insufficiency* It is possible, in exceptional instances, for the blood sodium to remain normal under the very conditions in which subnormal values almost always obtain. In one of the patients in the present series the blood sodium level did not drop below 136.6 milli-equivalents despite a nine day regimen of salt deprivation, although the clinical picture was typical of adrenal cortical insufficiency and there was protracted vomiting during the salt deprivation test. In this case the blood chloride, glucose and urea nitrogen values also remained normal. Treatment with DCA and supplementary salt did not alter the clinical picture and the patient died. Postmortem examination

revealed tuberculous caseation of both adrenal glands. A report of Loeb, Atchley and Parsons (182), is of interest in this connection. These authors observed four Addisonian patients who showed striking loss of sodium which was rectified by treatment with sodium chloride at the time of their first hospital admission. Later, clinical manifestations of crisis appeared but the blood electrolyte values remained normal. Despite the administration of sodium chloride and glucose the patients died.

2 *Blood chlorides* The plasma chloride concentration proved to be a less reliable indicator of adrenal cortical insufficiency in the present series of patients than did the sodium concentration. Normal blood chloride values were obtained in three patients whose blood sodium content was definitely below normal. The values were 124, 114 and 128 milli-equivalents of sodium per liter, the corresponding chloride concentrations were 103, 102 and 100 milli-equivalents per liter respectively. This finding is consistent with the observation in the experimental animal that the excretion of urinary sodium exceeds that of chloride (183).

3 *Blood potassium* In the present series it was found that the blood potassium determination was of less diagnostic value than the blood sodium determination. An increased blood potassium content (over six m eq per liter), was encountered only in those patients in whom the sodium ion concentration was subnormal. In a few instances normal blood potassium values were obtained despite the presence of a blood sodium deficit. Similar observations were made by Loeb, Atchley and Parsons (182), who concluded that a decrease in the blood sodium concentration usually occurs before an abnormal accumulation of potassium appears. An increase in the plasma potassium also occurs in the following conditions: asphyxia, hemorrhage, various forms of shock, severe renal disease (181, 184).

4 *Effects of treatment* Blood electrolyte determinations are of considerable value in regulating treatment. Under-treatment is revealed by subnormal sodium values. Overdosage with DCA produces hypernatremia (blood sodium values of over 140 m eq /l) and hypopotassemia (values of less than 3.0 m eq./l). Blood chloride determinations are of less value since excessive DCA may sometimes produce marked hypochloremia instead of hyperchloremia (185). A determination of the blood sodium concentration is of help in deciding whether edema is due to hypernatremia or to blood protein deficiency.

B. Blood proteins

Reduction in the total blood proteins is of infrequent occurrence in Addison's disease, although hypoproteinemia was observed in this series in a few patients who presented stigmata of panhypocorticalism. The Tiselius electrophoresis studies recently carried out by McCullagh,⁷ Lewis and Clark (186), in patients with adrenocortical insufficiency revealed normal total protein values in all of nineteen patients with adrenocortical insufficiency studied by them. However, the albumin percentage of the total protein was definitely decreased in all cases.

⁷ This appears to be the only study of this type carried out on Addisonian patients (187).

and the globulin fractions usually showed some increase. Adequate treatment with DCA for long periods of time was followed by some increase in the albumin content, but a normal protein distribution resulted only after large amounts of cortical extract were used for a month or longer.

C Blood glucose, urea nitrogen and other chemical constituents

Subnormal or low normal blood glucose values were obtained in about 80% of the patients in the present series. Thus the diagnosis of Addison's disease should be considered when hypoglycemia is present. The hypoglycemia appeared to bear no relationship to the level of blood electrolytes.

Significant retention of urea nitrogen is encountered usually only in severe adrenal cortical deficiency. In the present series blood urea nitrogen values higher than fifteen mgm per cent were obtained only in those patients who were in crisis. The highest urea nitrogen content encountered was fifty mgm per cent.

The serum calcium, sulphate, phosphate, creatinine and uric acid content may be increased in adrenocortical insufficiency.

D Hematologic examination

The hemoglobin content and the erythrocyte count were increased in crisis due to hemoconcentration. In the course of treatment the values for both were lowered due to rehydration. These determinations provided a fairly reliable gauge of the degree of hemodilution attendant upon treatment which was frequently checked with hematocrit determinations. The erythrocyte sedimentation rate was of no specific value, except in the presence of active tuberculosis. The total leucocyte count was usually normal. Except for a moderate lymphocytosis in a few instances, the differential count was normal. Rogers and Craig (188) recently reported similar findings. De la Balze, Reifenshein and Albright (189) found a definite relative neutropenia and a slight relative lymphocytosis in all of twenty Addisonian patients.

E Gastric analysis, urinalysis

About fifty per cent of Addisonian patients have achlorhydria. Urinalysis discloses a tendency toward low fixation of specific gravity in adrenocortical insufficiency. Maximum concentration is usually not obtained even when obvious dehydration is present (cf II F).

F Biopsy of skin

Histological examination of pigmented skin or mucous membrane reveals the presence of melanin. This pigment is found chiefly in the basal cells of the epidermis in the skin, whereas in the mucous membrane the melanin is encountered more frequently and in greater abundance in the sub-epidermal connective tissue (190). The differentiation between melanin and other pigments is possible with histochemical methods, but the deposition of melanin as described is not pathognomonic of Addison's disease.

G Tests of adrenocortical function

1 *Estimation of desoxycorticosterone activity.* The salt deprivation test discussed above (24) appears to offer the most reliable means of establishing the diagnosis of Addison's disease. There are two other tests which are frequently employed to estimate the electrolyte and water regulating ability or desoxycorticosterone activity of the adrenal cortex. These tests described by Cutler, Power and Wilder (191) and Robinson, Power and Kepler (192), respectively, have been considered to be a less reliable indicator of adrenocortical insufficiency than the sodium chloride deprivation test (14). A similar impression was obtained from the limited use of these tests in the present series. The test described by Robinson, Power and Kepler offers an advantage over the other two in that the patient is not exposed to the possible dangers of sodium deprivation.

2 *Glycogenic corticosteroid and 17-keto-steroid excretion.* In Addisonian patients of either sex there is a marked reduction in urinary 17-keto-steroids and 11-oxy-corticosteroid-like substances (193, 194, 195). However, a similar reduction in the excretion of these hormones occurs in other diseases, e.g., hypothyroidism and panhypopituitarism (193, 194). Determination of the excretion of the hormones under consideration can therefore yield only corroborative evidence or serve as a screening test for Addison's disease. Its value in the latter capacity is enhanced by the fact that the administration of 11-desoxycorticosterone acetate does not influence the assay values of the glycogenic corticoids (195).

3. *Response to pituitary adrenocorticotrophic hormone.* Thorn, Forsham, Prunty and Hills (196), have recently described a test employing the use of pituitary adrenocorticotrophic hormone which appears to be a measure of the adrenal reserve of hormones regulating carbohydrate fat and protein metabolism. This test is based on the observations that patients with classic Addison's disease failed to show either the marked fall in circulating eosinophilic leucocytes or the increase in urinary uric acid excretion which occurs in normal subjects following the intramuscular injection of adrenocorticotrophic hormone (131). The increase in urinary uric acid excretion is expressed as a change in uric acid creatinine ratio. "False positive" reactions occur in conditions associated with acute stress, or with decreased renal clearance or abnormally high production of uric acid. The eosinophile count and the uric acid creatinine ratio may both be affected in stress reactions, but in the other conditions the normal decrease in eosinophiles is noted. Thorn, et al. state that as a screening test their procedure supplements but does not necessarily correlate with the tests which estimate desoxycorticosterone activity. It appeared to correlate best with the excretion of 11-hydroxy-steroids. The injection of 30 mgm. of a water-soluble desoxycorticosterone glucoside caused neither a decrease in the eosinophile count nor a significant increase in the uric acid creatinine ratio.

a. *Response to epinephrine.* Long and his co-workers (197) demonstrated an adreno-cortical response in rats following the injection of epinephrine very similar to that obtained in the animals after the injection of adrenocorticotropin. The epinephrine effect depended on the presence of an intact anterior pituitary.

lobe Recant, Forsham and Thorn (198) recently noted a similar adrenocortical response in humans following an infusion of epinephrine. This consisted of a drop in the eosinophil count in normals, but practically no change in circulating eosinophils in patients with pituitary insufficiency. In patients with Addison's disease there was a definite but variable response which correlated approximately with the severity of the Addison's disease clinically. The studies suggested that it was possible to use the epinephrine response to differentiate between primary adrenal and pituitary-adrenal insufficiency.

IV TREATMENT

A Five phases of development

The empirical use of iron, arsenic, strychnine, and quinine as employed by Addison (199) remained the principal treatment for 33 years after the disease was described. The second phase of development, marking the beginning of replacement therapy in the disease, started with the use of adrenal extracts in 1892 and the recognition in 1895 of an active principle in the extracts (200-203). The latter was soon identified as epinephrine and was obtained in crystalline form and prepared synthetically shortly thereafter (204-206). However, the extracts were probably ineffective and epinephrine served chiefly to retard the development of Addisonian therapy since it diverted attention from the cortex. The third phase of development, the preparation of potent cortical extracts in the late 1920's (207-209), finally made a really effective measure available. Improved methods of extraction resulted in extracts of increased potency including the recently prepared carbohydrate-active lipo cortical extract (211-213) derived from hogs. The rationale of the electrolyte or fourth phase of therapy was established in 1932 (214-216) (8, 24) although sodium salts were demonstrated to have a beneficial effect as early as 1925 (217-219). The first practical maintenance measure was now provided, a synthetic hormone for similar purposes was soon to be added. The preparation of potent cortical extracts led to the fifth phase of Addisonian therapy—the isolation of a large number of crystalline corticosteroids (220-222) and the synthesis of desoxycorticosterone in 1937 (223). The subcutaneous implantation of pellets of the acetate of this potent hormone proved to be the most practical and convenient method of administration although other routes were also effective (224-227) (98). Dangers inherent in the action of the synthetic hormone (228-230), were avoided by a method of implanting less than the required number of pellets, and by giving small daily supplements of salt by mouth (97, 98). A small percentage of patients also require cortical extract for maintenance, almost all require the extract during crisis. The current therapy of Addison's disease combines the use of DCA, sodium salts and cortical extract.

B Treatment of patients in the present series

The treatment of the fifty patients in the present series during the twenty-two year period from 1924 to 1946 recapitulates the therapy of Addison's disease during all of the stages of its development.

1. *Early replacement therapy* The first six patients in the present series were admitted to the hospital between the years 1924 and 1931. At that time epinephrine injections and the oral administration of adrenal extracts were in use. However, only three patients received this form of therapy, all of whom died within ten days. The fourth patient, who survived twenty days, received infusions of five per cent glucose in saline and intravenous injections of fifty per cent glucose on an empirical basis. He was also given sodium cacodylate, one of the empirical measures used by Addison. Two patients received no specific treatment, the diagnosis not having been made ante-mortem.

2. *Cortical extracts.* Two patients in the present series admitted in 1932, were treated solely with adrenal cortical extracts parenterally. Table III shows that the average period of survival was eight and a half weeks as compared with eight days during the previous phase of therapy. In addition, both patients were brought out of crisis several times despite the fact that the extract was much less potent and a much smaller amount was used than is now employed. Extracts of higher potency became available soon after this, but by that time sodium salts were already in use, and consequently the patients treated henceforth were given both types of medication.

There is no doubt of the value of adrenal cortical extracts in Addison's disease. These extracts are capable of rescuing the patient in crisis and of maintaining the patient during intercritical periods in moderately good health. They are superior to desoxycorticosterone since they contain several active cortical factors. All cortical extracts may be expected to have some influence on intermediate carbohydrate metabolism, a property which desoxycorticosterone acetate does not possess, and the recently prepared lipocortical hog adrenal extract contains a considerably higher concentration of the carbohydrate-active oxycorticosterones. However, the use of cortical extracts is not without disadvantages, the most important of which are the limited supply and the high cost. As a result, the use of cortical extract is practically limited to the treatment of crisis.

3. *Electrolyte phase* The oral administration of sodium chloride was the first measure used freely in the maintenance of the Addisonian patient during intercritical periods. It was also effective in the treatment of crisis, though of less value than potent cortical extracts.

One patient who received salt as the only therapeutic measure lived three months. This patient entered the hospital in impending crisis and was markedly improved following administration of large amounts of sodium chloride. He was discharged with instructions to continue on this treatment and to return for "follow-up" observation. This he failed to do. Later, it was learned that he died in Addisonian crisis in a hospital in another city. Although this is the only patient (Table III) in whom salt was the sole measure used, four other patients were maintained in good health for twelve to thirty-nine months on large amounts of sodium salt. These patients all entered the hospital in adrenal cortical insufficiency. Following the addition of synthetic desoxycorticosterone acetate they survived for an additional fourteen months to seven and three-quarter

years The results obtained in three other patients may also be mentioned here These patients were treated by implantation of DCA in the form of pellets which weighed about 125 mgm each and which are known to last about one year They received daily oral supplement of sodium chloride Implantation was repeated after a period of two years Hence these three patients were maintained for at least six months and probably from nine to twelve months on salt alone in the form of a daily supplement of eight grams Toward the end of the two-year period there was a moderate weight loss and a recurrence of asthenia Long periods of survival on maintenance with salt alone and good results in the

TABLE III
Increase in the period of survival with progress in therapy

YEAR	THERAPY	NUMBER OF PATIENTS TREATED	PERIOD OF SURVIVAL*	
			Range	Average
1924-31	Suprarenal extract per os Epinephrine Injections	6†	1-20 days	8 days
1932	Weak cortical extract parenterally	2	4½-13 weeks	8½ weeks
1932-35	Sodium salts alone or with weak cortical extract	10‡	2-39 months	18 months
1935-39	Potent cortical extract and sodium salts	9	2 months to 8 years	2½ years
1939-47	Desoxycorticosterone acetate Sodium salts Cortical extracts	27	1 month to 11 years	4½ years

* From the date of diagnosis

† Two patients received no specific therapy because the diagnosis was not made antemortem The period of survival in these patients equals the period of hospitalization

‡ Four patients who survived for 12 to 39 months on salt therapy alone and later received combined therapy are included in both groups

treatment of crisis in some cases with sodium chloride alone have been reported by others (209, 14)

The requirement of cortical extract during crisis can be reduced by giving sodium chloride (231) Likewise, the maintenance requirement of DCA can be decreased, thus lowering the incidence of toxic effects (97, 98) However, it is not possible to maintain normal blood electrolyte levels in all Addisonian patients with sodium salts alone (183), the addition of cortical hormone is sometimes essential and always desirable Nine patients in the present series who were treated with salt as a maintenance measure and cortical extract during crisis survived for an average period of two and one-half years

4 *Desoxycorticosterone* The synthesis of this steroid in 1937 made available an easily administered and inexpensive hormone capable of regulating the electrolyte and water balance in the majority of Addisonian patients As a result this hormone has become the best practical measure in maintenance and is also of considerable value in the treatment of crisis

The lack of effect of DCA on the intermediary carbohydrate metabolism represents a source of danger since its administration improves the patient's muscular activity, but does not alter the intermediary carbohydrate metabolism. As a result, an increase in physical activity following the use of DCA may lead to hypoglycemic attacks. The absorption of excessive amounts of the synthetic steroid can result in arterial hypertension, edema, cardiac failure, and death. These effects are probably due to the sodium-retaining action of the DCA. The influence of this hormone on the excretion of potassium may also play a role in the development of heart failure. The more common symptoms of hypokalemia (anorexia, headache and muscular weakness) may lead to the erroneous administration of additional DCA. These shortcomings of DCA can be largely overcome, as will appear below.

5. *Combined therapy* The present treatment of Addison's disease utilizes a combination of cortical extract, sodium chloride and DCA. This will be illustrated in the present series.

a. *Treatment of crisis* Specific therapy was started without delay and the diagnosis corroborated later⁸ if a patient appeared to be in Addisonian crisis. Twenty c.c. of cortical extract were injected intravenously, an additional 20 c.c. were added to an intravenous drip of five per cent glucose in saline, and ten c.c. were injected subcutaneously. The extract was given in this manner to assure an adequate supply of hormone from the subcutaneous depot in the event that the intravenously injected extract were rapidly excreted in the urine. Five to ten mgms. of DCA⁹ in oil were injected intramuscularly, the amount depending on the degree of shock and the quantity administered prior to admission. Fifty c.c. of fifty per cent glucose were injected intravenously and more recently five c.c. of lipocortical extract were given subcutaneously to counteract hypoglycemia. Warm blankets were applied for shock and oxygen administered if respiration was rapid and shallow or cyanosis was present. Morphine was not given because of the sensitivity of Addisonian patients to this drug.

Sulfadiazine by intravenous injection, penicillin intramuscularly, or both, were given promptly in all patients who presented any evidence of infection.¹⁰ Sulfadiazine was used frequently and with good results (232) and is still employed when penicillin is ineffective. The equivalent of sodium used in conjunction with the sulfonamide drug was subtracted from the daily salt supplement.

Cortical extract was given every two to four hours until the crisis was definitely over, the frequency and the amount varying with the patient's course. The blood pressure was determined hourly. An additional 5 mgm. of DCA in oil was given after four hours if the blood pressure had not risen. Adrenalin, ephedrine and

⁸ Before any treatment was given, blood was drawn and set aside for hematological and chemical examinations.

⁹ The desoxycorticosterone acetate used in the treatment of the patients in this series was generously supplied by the Ciba Pharmaceutical Company.

¹⁰ The anti-bacterial drugs were given with considerable benefit to fourteen of twenty-seven patients treated with DCA.

coramine were given as vasopressors and to stimulate the respiratory center if required. The outcome was usually fatal if the patient failed to respond within six to eight hours. Some improvement was observed within six hours in the majority of cases. This was manifested by an improvement in the patient's appearance, an increase in the blood pressure, and a slowing of the pulse despite a frequent rise in temperature.

The patient was constantly observed for evidence of edema, both peripheral and pulmonary, since fluid and salt were being given in large amounts in conjunction with DCA. Hemoglobin and hematocrit determinations were of aid in detecting excessive hemodilution. The patient's condition was definitely improved as a rule at the end of twelve hours. Nevertheless, the slow intravenous administration of isotonic glucose and saline was continued and additional cortical extract was given. A total of 100 to 200 c c of cortical extract and 10 to 20 mgm of DCA were given in the first twenty-four hours. The amount of intravenous fluid was usually limited to 2500 c c over the same period. The flow of the intravenous drip was slowed and DCA was discontinued or given in smaller amounts if there was evidence of edema. However, this did not contraindicate the continued use of adrenal cortical extract. In the presence of persistent infection, 20 to 60 c c of adrenal cortical extract were given daily in divided doses, subcutaneously or by slow intravenous drip. The patient was also given daily injections of DCA in 3 to 5 mgm amounts depending on the severity of the infection, the blood pressure, and the state of hydration. Transfusions of citrated whole blood were given if the infection was prolonged or debilitating. The use of cortical extract was gradually eliminated following subsidence of the crisis and the infection. The parenteral administration of fluids was discontinued when the patient was able to retain fluid by mouth. Then 2 to 6 grams of sodium chloride was given by mouth daily and the amount of DCA was gradually reduced until the maintenance dosage was reached.

b Treatment of cerebral manifestations Since patients with acute cerebral symptoms usually had serious adrenocortical insufficiency they were treated as though they were in crisis. In addition, they received large amounts of the soluble B Vitamins parenterally and recently hypocortical (hog) extract. The latter was given in 5 c c amounts a few times daily for severe symptoms or in smaller doses otherwise. Oxygen was administered if high fever or shock were present.

Sedatives were employed cautiously and only if the patient was unmanageable. The drugs of choice were paraldehyde in 15 c c quantities, or chloral hydrate in 1 gram doses given by rectum. Morphine or the administration of barbiturates in large amounts or by parenteral injection was found to be dangerous. Marked regression of mental changes usually followed successful specific treatment, although some symptoms may have persisted for several days after restoration of the blood electrolytes and sugar. Maniacal behavior or convulsive seizures which did not respond to replacement therapy usually terminated fatally.

c Maintenance therapy 1 *DCA requirements* Treatment was always started in the hospital. The patient was placed on a fixed daily supplement of 4 grams of

salt and a daily intramuscular injection of 3 to 5 mgm of DCA was given until the systolic pressure was elevated to 100 mgm. Hg or signs of excessive water retention appeared. The amount of DCA was gradually reduced until the lowest dosage was reached which maintained the blood pressure, weight and strength. The daily requirement usually decreased within two weeks from 5 to 2 mgm. or less. The patient was then taught to inject the hormone and allowed to treat himself at home, returning for observation at frequent intervals to the Follow-Up Clinic. An undue increase in blood pressure, excessive gain in weight or fall in hemoglobin or hematocrit value was treated by discontinuing the use of synthetic hormone for two to three days and then by giving a somewhat smaller amount. Conversely, the amount of hormone was increased if signs of undertreatment appeared. DCA was found to be very potent. The addition or subtraction of 0.25 mgm. in the daily dose produced discernible effects within a few days. The steroid was given suspended in peanut oil, each cubic centimeter of oil containing 5 mgm. of the steroid, a tuberculin-type syringe was used because of the small quantity injected. A daily maintenance dose of 1 to 1.5 mgm. of DCA was found to be adequate in most patients after three to six months of observation. No patient receiving supplementary salt required more than 1.5 mgm. of the synthetic hormone daily.

2 *Pellet requirements.* The most convenient method of administering DCA is the subcutaneous implantation of pellets after the minimum daily requirement by injection has been determined over a period of four to six months. This period of observation is necessary since the initial requirement may far exceed the minimum requirement. In two patients given implanted pellets calculated to fulfill the initial requirement toxic effects were noted despite adjustment of the daily salt supplement which ordinarily provides flexibility in the post-implantation treatment. The toxic effects disappeared when the surplus pellets were removed (97). The number of pellets implanted is based on the calculation that a pellet weighing 125 mgm. yields about 0.3 mgm. each day, and that the daily requirement by pellet is about sixty per cent of that by injection. Thus patients who were maintained in good health with a daily injection of 1 mgm. of DCA required the implantation of but two pellets. Ten patients in the present series were implanted with pellets, none with more than four.

3 *Pellet implantation.* The patients were readmitted to the hospital for implantation. Preoperatively 5 c.c. of cortical extract, in two equal doses, and 2.5 mgm. of DCA were injected. Sedation of all types, especially morphine, the "routine" preoperative measure, was deliberately avoided. The pellet implantations were carried out under surgical conditions. Small subcutaneous pockets were made, under local anesthesia, in the skin beneath the scapulae. A separate pocket was made for each pellet since extrusion of pellets sometimes occurs. The pockets were closed with silk sutures. Despite the superficial nature of the procedure, one patient developed mild shock shortly after the implantation. This responded well to an infusion of 500 c.c. of isotonic saline solution and 5 c.c. of cortical extract intravenously. In a few instances, suppuration developed

in the implantation pocket and the pellet was extruded, occasionally this occurred without evidence of suppuration. The prompt administration of penicillin served to preserve the implantation in two patients.

The patient was kept under observation in the hospital for at least a week after implantation. The daily injection of synthetic hormone was stopped, but small quantities of cortical extract were given for two to three days and the administration of salt was continued. Following discontinuation of the cortical extract, the effect of the implanted DCA was evaluated by the patient's general well-being, weight, blood pressure, hemoglobin, hematocrit and blood electrolyte values. In three patients there was transitory elevation of blood pressure and mild edema which regressed several days after the supplementary salt had been reduced or discontinued.

The patient was discharged from the hospital when the blood pressure and weight became stable. He returned for monthly observation in the Follow-Up Clinic where adjustment was made in the salt supplement to provide for the extra needs during hot weather or if a mild infection were present.

4 *Pellet depletion* A gradual recurrence of signs and symptoms of adrenal cortical insufficiency which appeared approximately twelve to fourteen months after implantation marked the depletion of the pellets. This was confirmed by inspection. The symptoms were delayed in three patients for as long as two years by increasing the supplementary salt to eight grams daily. However, these patients were less resistant to respiratory infections and withstood the hot weather less well during the second year. It is significant that symptoms of adrenocortical insufficiency appeared one to two months before the blood electrolyte values were significantly altered. As a rule, reimplantation was carried out annually, unless signs of cortical insufficiency appeared earlier.

5 *Re-implantation of pellets* The daily salt supplement was increased and arrangements made for re-implantation when evidence of pellet depletion appeared. The daily maintenance dose of DCA was redetermined by subcutaneous injections over a period of several weeks before readmission to the Hospital if the basal requirement appeared to have changed. The same number of pellets were usually re-implanted, the procedure was carried out in the same manner as the original implantation. The previous implantation site was explored in some patients. The pellets were gone after twelve to fourteen months or else were so small they could be disregarded in determining the amount of hormone to be re-implanted. However, in one patient tiny fragments were found after eighteen months. Eight patients have been given reimplantation a total of twenty-seven times.

6 *Maintenance with DCA injections* Seventeen of the twenty-seven patients who were treated with DCA received the hormone by injection alone. Five patients died early in the course of their illness, before maintenance therapy was established. The remaining twelve patients were not treated by implantation because they required minor doses of DCA, had complications resulting in frequent fluctuations in the DCA requirement, or suffered from coexisting

diabetes or multiglandular endocrine insufficiency necessitating other injections. Five patients preferred not to have implantation, two reported that they were well with injections of 5 mgm. every three to four days.

7. *Use of cortical extract in DCA treated patients.* Cortical extract was administered to eighteen of the twenty-seven above patients principally during crisis, but also as a supplement in maintenance therapy.

d *Treatment of coexisting endocrine disease* 1 *Diabetes mellitus.* The two patients in the present series with combined Addison's disease and diabetes mellitus provided the opportunity of gathering some observations in the treatment of this rare combination. These observations are of additional interest since the patients¹¹ represented opposite extremes in the severity of their illnesses and in the difficulty in management.

The Addison's disease was treated as previously outlined. There was an additional problem in the treatment of the diabetes arising from the marked sensitivity to insulin which was present despite hyperglycemia and glycosuria. Thus insulin was given sparingly and only if there was ketonuria, weight loss due to glycosuria, or if the latter was marked. Protamine zinc insulinate was tolerated better than plain insulin. The carbohydrate-active lipo-cortical extract reduced the sensitivity to insulin making it possible to use somewhat larger amounts of insulin in the treatment of diabetic ketosis. Mild glycosuria was found to be beneficial. The administration of sodium chloride and the salt and water-retaining DCA helped to prevent polyuria and the loss of base which might otherwise accompany the glycosuria.

2 *Hypothyroidism.* Two patients in the present series exhibiting manifestations of hypothyroidism and Addison's disease were treated with thyroid extract in addition to the other measures. The thyroid gland substance was well tolerated. It was given in doses of one tenth of a grain initially and was gradually increased to one grain daily. There was discernible improvement in the patient with typical myxedema, but this was not striking. No improvement was observed in the other patient.

3 *Hypogonadism.* As previously mentioned, injections of testosterone had no discernible effect on the two men who complained of impotence.

4 *Panhypocorticalism.* Three patients presenting evidence of multiglandular involvement responded better when small daily injections of cortical extract were added to the usual maintenance measures. Somewhat smaller amounts of DCA and salt were used because of an increased tendency to edema. Two of the patients received thyroid substance and male sex hormone as mentioned above. Iron proved to be of limited value in treating a secondary type of anemia in these patients.

e *Advantages of maintenance therapy.* The maintenance measures used endowed the patients with a greater ability to withstand illnesses which commonly precipitate crisis in untreated patients. These included moderately severe upper respiratory infections and gastro-enteritis. Minor surgical procedures were well tolerated with but a small increment in salt and DCA. The patients receiving

¹¹ Patients W. C., table IV, and K. M., table V.

maintenance therapy were less affected by severe illness associated with high fever, required smaller amounts of cortical extract during such illness and recovered more rapidly. The severe illness and especially those which terminated fatally¹² occurred more frequently in patients who had not received proper maintenance therapy.

Furthermore, the patients could be restored to useful activity as illustrated in Table IV. A fifty-five year old bookkeeper returned to his employment after having been idle for seven years. A fifty-three year old woman is now able to perform all of her household duties after the second implantation of pellets. She had been semi-invalided for four and a half years previously. A forty-six year old motorman has diabetes mellitus in addition to Addison's disease. This man has had no difficulty in carrying out his work as a "yard" motorman and,

TABLE IV

Desoxycorticosterone acetate maintenance therapy, patients currently receiving treatment, restoration to useful activity

PATIENT	AGE	SEX	SURVIVAL	TYPE OF WORK
			<i>years</i>	
J G	41	M	11	Carpenter
S R	29	M	10	None
E B	50	F	10	Housewife
J C	53	M	9	Bookkeeper
L C	44	M	9	Able to do light work
E M	50	F	8	Housewife
W C	46	M	7	Motorman
B S	33	M	5	Salesman
F G	53	F	3	Housewife
H W	46	F	3	Housewife
S R	27	F	2	Housewife

despite urgent admonitions to the contrary, has continued to play baseball each summer. One patient, not included in table IV, who succumbed to a severe infection after 3½ years of treatment, drove a taxi up until three days before his death.

f Shortcomings of maintenance therapy Despite the treatment now in use, the Addisonian patient remains more susceptible to infection and less tolerant of intercurrent illness than normal persons. His tendency to hypoglycemia is only partly checked by maintenance therapy. The treatment apparently does not prevent development of multiglandular involvement, nor the progressive deterioration which accompanies it. Mental changes appeared in several instances despite adequate sodium chloride and DCA administration and normal blood sodium values. Although restoration to useful activity was achieved in almost all of the patients receiving maintenance therapy, none of the patients was restored completely to normal.

¹² An analysis of the deaths of the patients who received DCA is given in table V.

TABLE V

Desoxycorticosterone acetate therapy, cases with fatal outcome

PATIENT	AGE	SEX	PERIOD OF SURVIVAL	SURVIVAL ON DCA THERAPY	PROBABLE CAUSE OF DEATH	COMMENT
1 G K.	37	M	3½ yrs.	1½ yrs	Active pulmonary tuberculosis	Therapy effective until bi-lateral apical spread developed
2 H J	36	F	3 mos	3 mos	Bronchopneumonia*	†
3 F L	48	F	1 mo	1 mo	Acute cardiac insufficiency	Died suddenly Diffuse focal myocardial necroses Multiglandular involvement*
4 C G	35	F	5½ yrs	3 yrs	Bronchopneumonia†	
5 E C .	50	F	3½ yrs	3½ yrs	Post-operative shock	Phlegmonous cholecystitis†
6 N R	38	M	3½ yrs	3½ yrs	Severe pharyngitis	Last implantation 2 years prior to death
7 E K	62	F	2 mos	2 mos	Acute coronary insufficiency§	Protracted vomiting despite normal blood Na and DCA therapy Coronary arteriosclerosis* Patient had been psychotic
8 S K	60	F	4½ yrs	4½ yrs	Upper respiratory infection	
9 C B	37	F	1 yr	1 yr	Severe nasopharyngitis	Multiglandular endocrine involvement*
10 S K	35	F	4½ yrs	4½ yrs	Suppuration at site of DCA injection*	Injection given by inexperienced person at home†
11 H H	51	F	6 mos	6 mos	Pulmonary edema	Died suddenly Disseminated focal myocardial fibrosis, multiglandular endocrine involvement*
12. S G	56	F	1½ yrs	1½ yrs	Unknown‡	Died suddenly
13 D G	28	F	8½ yrs	7 yrs	Psychosis	Prolonged intensive combined therapy ineffective terminally
14 L R	35	F	3 mos	3 mos	Morphine sensitivity	Extensive hemorrhagic necrosis of adrenals*
15 J K	53	M	7½ yrs	7½ yrs	Adrenal and thyroid gland insufficiency	Myxedema and Addison's disease† Marked adrenal and thyroid atrophy Pituitary changes*
16 K.M	21	F	1 yr	1 yr.	Progressive encephalopathy with convulsive seizures	Combined Addison's disease and diabetes mellitus†

* Autopsy

† Also received intensive combined therapy

‡ Died elsewhere than at Mount Sinai Hospital

§ Clinical and ECG evidence

6 *Progress in therapy* Marked progress has been accomplished in the treatment of Addison's disease in the twenty-two years in which the fifty patients were treated. Table III shows that the average period of survival has been prolonged to $4\frac{1}{2}$ years. Table IV shows that the eleven patients who are still alive have survived for an average of seven years, and that almost all have been restored to useful activity.

7 *Relative value of therapeutic measures* The maximum period of survival was obtained with combined therapy, including DCA, sodium chloride and cortical extract. Antibacterial agents were often of vital importance. Sodium salts alone were less effective than either adrenal cortical extract or the synthetic DCA. Adrenal cortical extract appears to be a very effective means of treating all phases of the disease. However, DCA, by virtue of its abundant supply, its low cost, and the convenience of its use, was the most valuable practical measure in the care of the patient.

8 *Future* The recent synthesis of 11-dehydrocorticosterone and the current progress (233, 234) in perfecting methods of preparing 11-oxy-steroids synthetically indicate that a carbohydrate-active hormone¹³ may soon be available for clinical use. Cortical extracts of increased potency are to be expected, and more effective therapy may soon be available for concomitant endocrine gland disturbances. The newer antibiotics will probably help to reduce the danger of infection. In this lies hope of better chances of survival and of more complete restoration for the patient with Addison's disease.

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FUNCTIONING PANCREATIC ISLET CELL ADENOMAS¹

A REVIEW OF THE LITERATURE AND PRESENTATION OF TWO NEW DIFFERENTIAL TESTS

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INTRODUCTION

Insulin-secreting pancreatic islet cell adenomas, or insulinomas³ have been the subject of numerous reports during the past 25 years. Many of these have included excellent reviews of the subject, usually, however dealing with a special aspect of the problem. No one to date has attempted to survey comprehensively the many aspects of the subject. The present review analyzes the clinical and pathological features of 258 cases reported in the literature up to January 1, 1949.

In addition, two new and relatively simple laboratory procedures of value in differentiating hypoglycemia caused by lesions of the pituitary, adrenal cortex and pancreatic islet cells are described. These tests were helpful in studying a patient (158) with acromegaly in whom episodes of severe hypoglycemia following pituitary irradiation introduced a difficult problem in differential diagnosis between insulinoma and hypoglycemia secondary to pituitary-adrenal failure. In this instance two insulinomas were removed at operation,⁴ raising the interesting possible relationship between an excess of growth hormone and the development of multiple islet cell tumors.

Historical. The study of this subject had its origin in 1869 when Paul Langerhans (3), while still a medical student, wrote his brilliant treatise on the *inseln* or *les îlots de Langerhans*, as they were designated by Laguesse (4) in 1893. The latter initially suggested the possible endocrine nature of the islets, following the work of von Mering and Minkowski (5), who produced fatal diabetes in animals by complete removal of the pancreas.

In 1900 Ssobolew (6), on the basis of experiments in which he induced atrophy of the entire pancreas except the islet tissue without developing diabetes mellitus, postulated a substance from the islet cells as a possible therapeutic material for diabetic patients.

Nicholls (7) reported the first islet cell tumor in 1902, but gave no clinical history. Lane (8) differentiated the alpha and beta cells in 1908. Histological origin of the islet cells was clarified by Bensley (9) and Grauer (10) who demonstrated that the epithelial cells of the islands appeared to be derived from the

¹ This study was aided by funds from the Medical Surgical Research Fund of the Peter Bent Brigham Hospital.

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³ The term insulinoma is used throughout this paper to denote an insulin-secreting islet cell adenoma, insulinoma (1), or nesidioblastoma (2).

⁴ This case has been reported in detail elsewhere (158).

epithelial cells of the small ducts of the pancreas. Other theories have been proposed but most experts in the field adhere to the ductal origin.

The clinical vistas of this field were opened with the discovery of insulin by Banting and Best (11) in 1922 and the prompt finding by their co-workers, Campbell and Fletcher (12), of the symptom complex produced by insulin overdosage. Shortly thereafter Harris (13), Gibson and Larimer (14) and others postulated the occurrence of identical situations in patients suffering from spontaneous attacks of hypoglycemia.

W J Mayo (15) provided the first surgical proof of hyperinsulinism by his operation in 1927 on a physician with hypoglycemic symptoms, which were found to be associated with an insulin-secreting, metastatic carcinoma of the pancreas. Two years later the first surgical cure was accomplished by Graham (16) of Toronto by the removal of what was considered a malignant pancreatic islet cell adenoma; while the following year from this hospital Cushing (17) reported the first successful operation on a benign insulinoma.

For the past twenty years the major contributions on this subject have been made by Whipple and Frantz (18-22). In 1940 (20) and in 1944 (21) these authors recorded 147 cases from the literature. The largest personal series to date have been those of Lopez-Kruger (23) from the Mayo Clinic (38 cases) and of Whipple (27 cases). To these previous reports and reviews (24-37) have been added 111 (38-105) patients making a total of 258 cases of functioning islet cell adenomas. In reviewing this large group an attempt has been made wherever possible to obtain and summarize data with regard to the following categories:

1. Age of patients
2. Sex
3. Number of tumors
4. Size of tumors
5. Distribution of tumors.
6. Incidence of malignancy
7. Signs and symptoms of hyperinsulinism
8. Diagnosis
9. Differential diagnosis.
10. Associated endocrine abnormalities
11. Treatment

Age. Insulinomas may occur at any age, having been reported in patients from $6\frac{1}{2}$ weeks (82) to 68 years (23) of age. As may be seen in chart 1, the peak incidence lies between 40 and 50 years. Symptoms both as regards type and severity do not appear to differ significantly among the various age groups.

Sex. No significant sex difference exists in the incidence of benign tumors. Fifty-two per cent of the cases occurred in males and 48 per cent in female patients. Among the twenty-four instances of malignant tumors fifteen (63 per cent) were found in males.

Number of tumors. Although 206 patients or 88 per cent of those with benign adenomas had a single tumor demonstrated, it is of interest to note that in 12 per cent more than one tumor was discovered (table 1). In six patients diffuse

adenomatosis of either the entire gland or a portion of it was found, the tumors varying in size from microscopic to 3 cm in diameter (21, 23, 69, 107, 109) No preoperative diagnostic method is known which would indicate the presence of multiple tumors or diffuse adenomatosis To obviate subsequent surgical

AGE INCIDENCE OF 226 PATIENTS WITH INSULINOMA

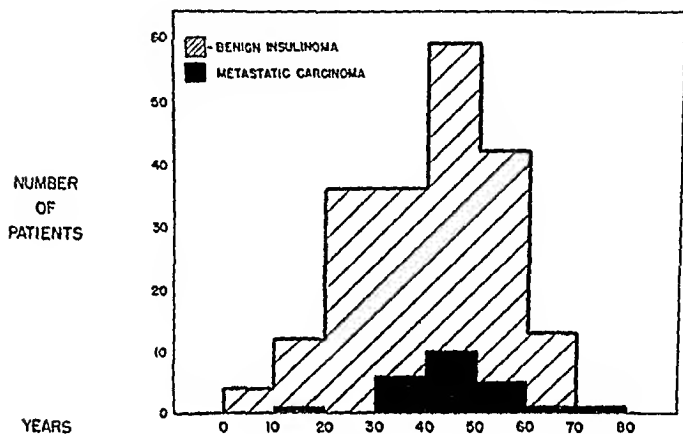


CHART 1

TABLE 1

Number of insulinomas in individual patients

	BENIGN	METASTATIC
Single	206	20
Multiple		4
2	15	
3	4	
4	2	
5	1	
Adenomatosis	6	

exploration, the surgeon must always consider the possibility of multiple tumors in any patient with definite signs of insulinoma.

Size of tumors Insulinomas varying in size from microscopic to 11 cm in diameter have been found, however, 75 per cent of those reported range from 1-3 cm in their greatest diameter (chart 2). Of the nine adenomas over 5 cm, four were questionably malignant. Symptoms were not found to vary significantly with the size of the tumor (106).

Distribution of tumors Earlier reports stressed the fact that the great majority

epithelial cells of the small ducts of the pancreas. Other theories have been proposed but most experts in the field adhere to the ductal origin.

The clinical vistas of this field were opened with the discovery of insulin by Banting and Best (11) in 1922 and the prompt finding by their co-workers, Campbell and Fletcher (12), of the symptom complex produced by insulin overdosage. Shortly thereafter Harris (13), Gibson and Larimer (14) and others postulated the occurrence of identical situations in patients suffering from spontaneous attacks of hypoglycemia.

W J Mayo (15) provided the first surgical proof of hyperinsulinism by his operation in 1927 on a physician with hypoglycemic symptoms, which were found to be associated with an insulin-secreting, metastatic carcinoma of the pancreas. Two years later the first surgical cure was accomplished by Graham (16) of Toronto by the removal of what was considered a malignant pancreatic islet cell adenoma, while the following year from this hospital Cushing (17) reported the first successful operation on a benign insulinoma.

For the past twenty years the major contributions on this subject have been made by Whipple and Frantz (18-22). In 1940 (20) and in 1944 (21) these authors recorded 147 cases from the literature. The largest personal series to date have been those of Lopez-Kruger (23) from the Mayo Clinic (38 cases) and of Whipple (27 cases). To these previous reports and reviews (24-37) have been added 111 (38-105) patients making a total of 258 cases of functioning islet cell adenomas. In reviewing this large group an attempt has been made wherever possible to obtain and summarize data with regard to the following categories:

1. Age of patients
2. Sex
3. Number of tumors
4. Size of tumors
5. Distribution of tumors.
6. Incidence of malignancy
7. Signs and symptoms of hyperinsulinism
8. Diagnosis
9. Differential diagnosis
10. Associated endocrine abnormalities.
11. Treatment.

Age Insulinomas may occur at any age, having been reported in patients from 6½ weeks (82) to 68 years (23) of age. As may be seen in chart 1, the peak incidence lies between 40 and 50 years. Symptoms both as regards type and severity do not appear to differ significantly among the various age groups.

Sex No significant sex difference exists in the incidence of benign tumors. Fifty-two per cent of the cases occurred in males and 48 per cent in female patients. Among the twenty-four instances of malignant tumors fifteen (63 per cent) were found in males.

Number of tumors Although 206 patients or 88 per cent of those with benign adenomas had a single tumor demonstrated, it is of interest to note that in 12 per cent more than one tumor was discovered (table 1). In six patients diffuse

adenomatosis of either the entire gland or a portion of it was found, the tumors varying in size from microscopic to 3 cm in diameter (21, 23, 69, 107, 109) No preoperative diagnostic method is known which would indicate the presence of multiple tumors or diffuse adenomatosis To obviate subsequent surgical

AGE INCIDENCE OF 226 PATIENTS WITH INSULINOMA

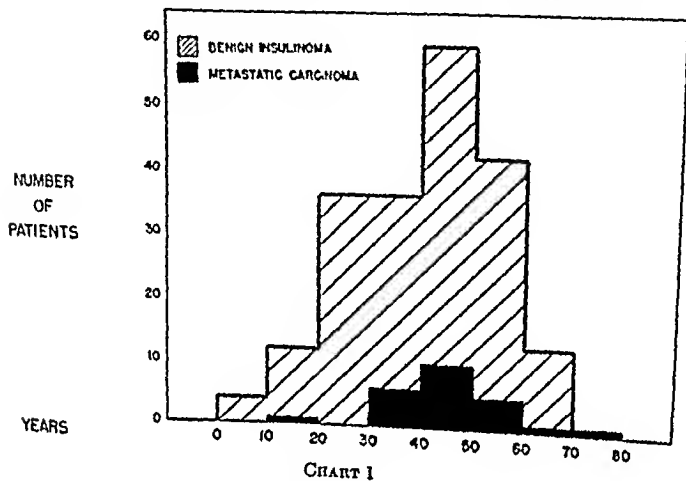


TABLE 1

Number of insulinomas in individual patients

	BENIGN	METASTATIC
Single		
Multiple	200	20
2		4
3	15	
4	4	
5	2	
Adenomatosis	1	
	0	

exploration, the surgeon must always consider the possibility of multiple tumors in any patient with definite signs of insulinoma

Size of tumors Insulinomas varying in size from microscopic to 11 cm in diameter have been found, however, 75 per cent of those reported range from 1-3 cm in their greatest diameter (chart 2) Of the nine adenomas over 5 cm, four were questionably malignant Symptoms were not found to vary significantly with the size of the tumor (106)

Distribution of tumors Earlier reports stressed the fact that the great majority

of insulinomas appeared to be located in the tail of the pancreas. In this review it is apparent that there is a wide distribution of tumors throughout the entire

SIZE OF 222 INSULINOMAS

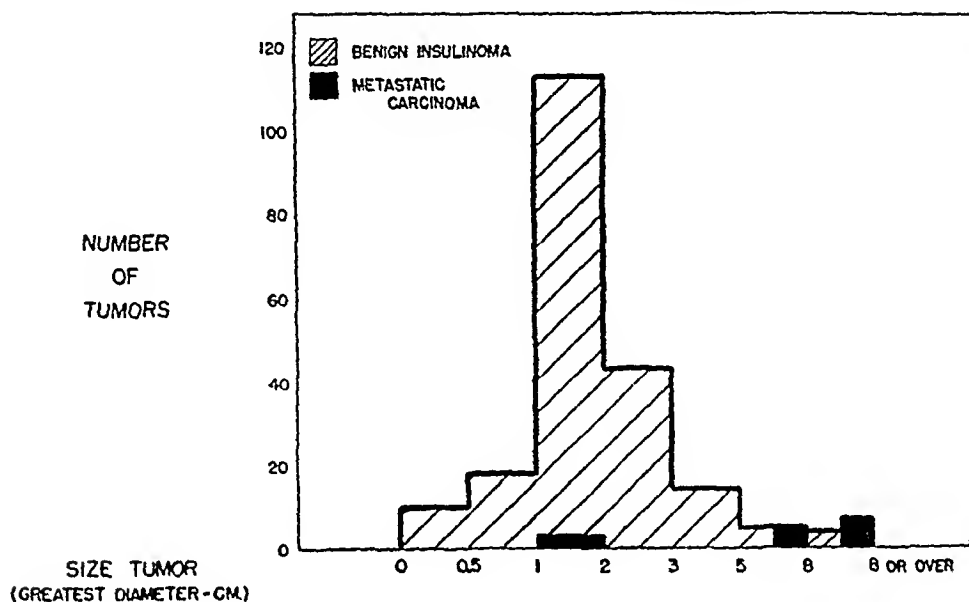


CHART 2

DISTRIBUTION OF INSULINOMAS IN PANCREAS

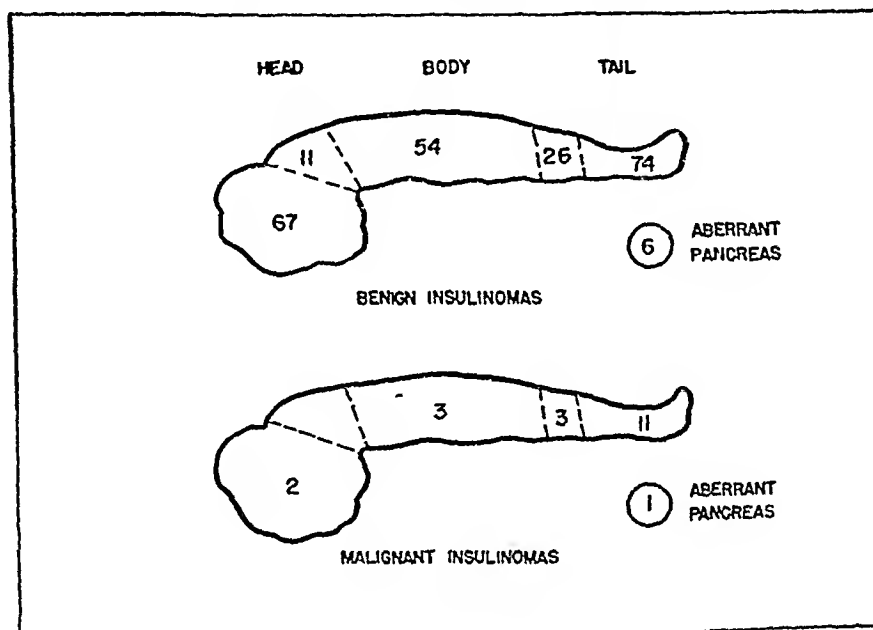


CHART 3

gland (chart 3) It is well known that tumors in the head of the pancreas lie deep in the substance of the gland (110), whereas, those in the body and tail lie nearer the surface. Surgical exploration of the head is much more difficult than that

of other portions of the gland. These facts and the misconception regarding the high incidence of tumors in the tail of the pancreas probably account for the large number of cases in which an initial surgical exploration of the tail of the pancreas only is carried out without relief of symptoms, whereas, subsequent operation with more extensive exploration of the entire gland often reveals an adenoma in the head or body of the gland. It is significant that the experience of the Mayo Clinic group (23) and Whipple (22) confirm this observation. It is also well to keep in mind that the tumor may be found in aberrant pancreatic tissue (111) as was the case in six patients in this series (23, 80, 85, 112-114).

The difficulty of finding the tumor and the advisability of re-operation if symptoms persist even after the successful removal of one tumor are attested by the fact that in this group of 258 cases, 19 patients required two operations before the tumor was removed. In three patients a third operation was necessary.

If no tumor is discovered, a decision must be made as to the advisability of resecting a portion of the pancreas. Results with this procedure have been

TABLE 2
Insulinomas reported up to 1949

	DISCOVERED AT		Total
	Operation	Autopsy	
Benign adenomas	157	33	190
? Malignant adenomas	13	1	44
Metastatic carcinoma	18	6	24
	218	40	258

disappointing, but as might be anticipated the best results have been obtained with more radical resections (35, 115, 116).

Incidence of malignancy. The pathological diagnoses among the 258 cases revealed 190 cases of benign adenoma, 44 cases characterized as questionably malignant and 24 cases of carcinoma with metastases (table 2). Thus in less than 10 per cent was the tumor definitely malignant.

Patients in this definitely malignant group (23, 24, 27, 30, 38, 58, 59, 77, 84, 91, 92, 100, 101, 113, 131-140) varied in age from 18 to 73 years and as a whole fall into a slightly older age group than did those with non-metastatic lesions (chart 1). In this series there were 15 males and 9 females. The tumor size was uniformly greater, with only three being between 1-2 cm. in diameter and the remainder over 5 cm. (chart 2). In 20 cases the initial lesion was single, whereas, in four cases it was multiple. Of the twenty single tumors only two occurred in the head of the gland, three occurred in the body, three at the junction of the body and tail, eleven in the tail, while one was aberrant in origin (chart 3). Although metastases may be found in almost any portion of the body, the liver appeared to be involved predominantly (table 3).

The diagnosis of malignant insulinomas is somewhat confused by the fact that 50 per cent of the reported cases of benign adenomas were shown to have an incomplete capsule. Initially it was thought an incomplete capsule, mitotic figures and/or blood vessel invasion were indicative of malignancy. However, data derived from the literature do not support these conclusions. Absence of the capsule per se is apparently of little significance unless this has resulted from invasive and destructive proliferation of tumor cells.

Of the tumors considered questionably malignant, nine were reported to have had blood vessel invasion by tumor cells, four had no invasion, and in thirty-one no note was made. Although there have been several five year follow-ups, only one of these tumors has been reported as recurring or metastasizing. Initially this case was recorded by Brunschwig (117) in 1941 as questionably malignant, however, two years later (118) the patient had recurrence of symptoms and died with metastases. Frantz (20, 21) has suggested that this variety of insulinoma may be analogous to the so-called "adenoma malignum" type.

TABLE 3
Sites of metastases in 24 patients with malignant insulinomas

ORGAN	NUMBER OF PATIENTS
Liver	23
Regional lymph nodes	12
Mesentery, peritoneum, epicardium adrenals, lungs, spleen	2
Pleura, vena cava, kidney, stomach, subcutaneous tissue, portal vein, spinal cord	1

of carcinoma of the thyroid gland where distant metastases might be late or slow in appearing.

Signs and symptoms of hyperinsulinism. A review of the signs and symptoms produced by insulinomas necessarily emphasizes the protean manifestations (124) of these tumors and the ease with which the diagnosis may be overlooked unless searched for carefully both by history and laboratory aids. The usual story is for patients with islet cell tumors to have been followed for a relatively long period in clinics specializing in neurology, gastroenterology, psychiatry, metabolism and endocrinology, before the underlying process is discovered and complete relief afforded by surgical extirpation.

The outstanding manifestations reported in 193 patients with insulinomas in whom a careful history was recorded are presented in table 4. Since many of these histories were taken during brief pre-operative surgical admissions, it is probable that the more obvious symptoms, such as convulsions and coma were reported in greater percentage than were the more innocuous ones such as sweating and lightheadedness.

Review of the symptoms and signs serves merely to illustrate that an insulinoma exhibits no pathognomonic symptom-complex. Furthermore no significant difference in symptomatology was found between benign or metastatic

tumors except in the one instance noted subsequently, thus making pre operative differentiation of a malignant and non-malignant insulinoma impossible Proof that an insulinoma is present must usually await laboratory studies

Symptoms of hyperinsulinism have been reported as being present from two weeks to over twenty years prior to operative intervention As can be seen from the accompanying chart (4), 25 per cent of patients had had symptoms for more than five years The duration of symptoms was much briefer in the group of malignant insulinomas, however with only 3 reported as having been affected for more than two years

TABLE 4

Signs and symptoms exhibited by 188 patients with insulinomas

	<i>per cent</i>
1 Loss of consciousness	58
2 Confusional state	54
3 Weakness and fatigue	41
4 Deep coma	40
5 Sweating	36
6 Drowsiness and stupor	35
7 Lightheadedness	30
8 Visual disturbances	30
9 Amnesia	28
10 Clonic convulsions	24
11 Noisy behavior	20
12 Headache	20
13 Tremor	18
14 Hunger	14
15 Positive Babinski	13
16 Paresthesias	13
17 Irritability	11
18 Transient hemiplegia	10
19 Abdominal pain	8
20 Palpitation	3

The fact that the overall respiratory quotient of nervous tissue is 0.98-1.00 (125-127) suggests that its metabolism is predominantly that of carbohydrate Since nervous tissue has the highest R Q of any system in the body and, therefore, presumably the greatest need for carbohydrate, it would follow that the major changes occurring in severe hypoglycemia would be nervous in origin A very complete and excellent review of this subject has been written by Fabrykant and Bruger (128) Over fifty per cent of the patients with insulinomas suffered loss of consciousness or developed confusional states Deep coma occurred in 95 per cent with metastatic lesions, whereas, only one third of patients with benign tumors were so effected This was the only striking difference between benign and malignant lesions and may be explained in part on the basis of additional hypoglycemia from reduction in liver parenchyma secondary to metastases The high incidence of confusional states, clonic convulsions, loss of continence, amnesia, etc., serves to stress the importance of differentiating

patients with insulinomas from those with idiopathic epilepsy or suspected brain tumors. A 10 per cent incidence of hemiplegia makes insulinoma a lesion seriously to be considered in any patient with hemiparesis. Although twelve patients were thought to have irreversible personality changes with mental deterioration, seven of these were restored completely to normal following successful operation (table 5). Other manifestations of central nervous system

DURATION OF SYMPTOMS IN 193 PATIENTS
PRIOR TO DISCOVERY OF INSULINOMA AT OPERATION OR AUTOPSY

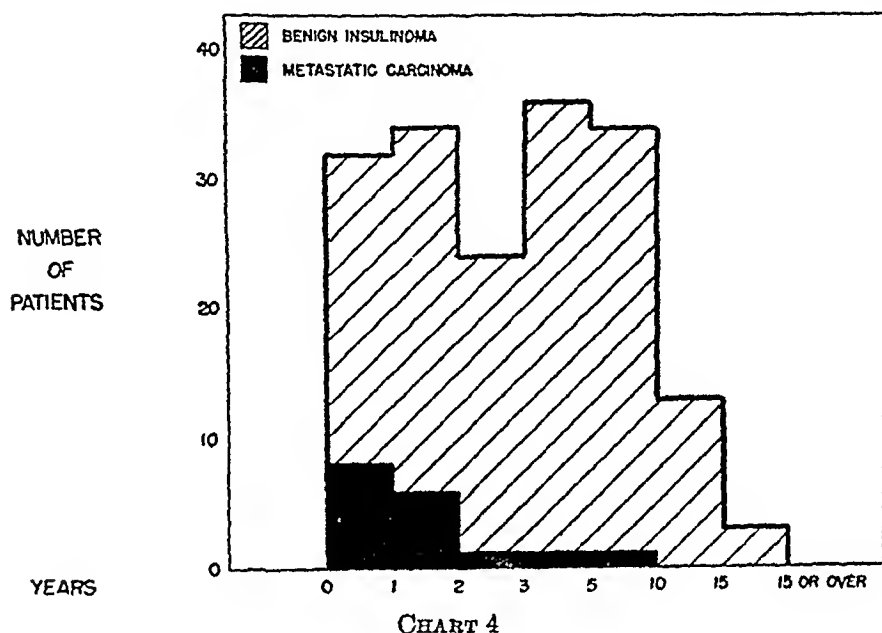


CHART 4

TABLE 5

Residual postoperative findings in 183 patients presumably cured of insulinomas

Permanent central nervous system damage	3
No relief of symptoms	3
Unreliability	2
Residual palsy	2
Occasional low blood sugars	2
Anxiety state	1
Blurred vision	1
Muscle atrophy	1

disorder produced primarily by hypoglycemia include inability to speak properly, purposeless movements, incoordination, silliness or negativism, twitchings, incoherence, mental dullness, tonic convulsions, petit mal, Jacksonian sensory seizures, and in one instance permanent hemiplegia. The surprisingly low incidence of hunger as a symptom will be discussed further in the section on changes in body weight.

The importance of epinephrine in combatting hypoglycemia by facilitating the liberation of liver glycogen to glucose (increased glycogenolysis) is well substantiated (129-130). With very severe hypoglycemia however, such large

quantities of epinephrine may be mobilized that symptoms of hyperadrenalinism such as sweating, tremor, pallor, coldness, palpitation, and precordial oppression may dominate the clinical picture. Not infrequently these may be the only symptoms found in a patient with an insulinoma.

Another group of symptoms appear to result from the combination of hypoglycemia and hyperadrenalinism. Among these are weakness and fatigue, lightheadedness, and visual disturbances which occurred in over 30 per cent. The visual difficulties included blurred vision, diplopia, dimness of vision, colored vision, scotomata, transient blindness, nystagmus, visual hallucinations,

LOWEST BLOOD SUGAR LEVEL RECORDED IN 201 PATIENTS WITH INSULINOMA

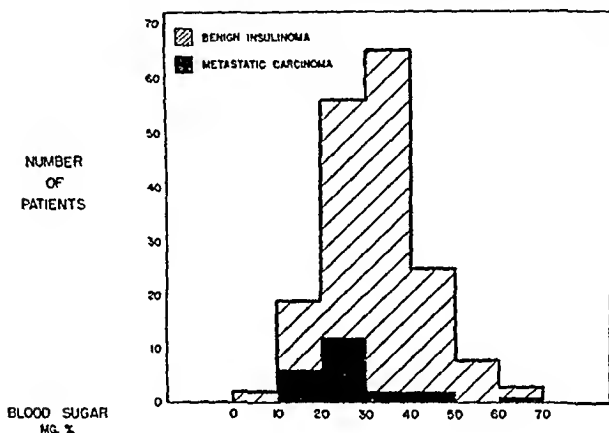


CHART 5

hemianopsia, and oculogyric spasms. Falling in this group also, but not mentioned in the table are circumoral paresthesias, inability to concentrate, and vertigo.

Thirty per cent of patients with metastatic insulinomas complained of abdominal pain. This was present in only 6 per cent of patients with benign adenomas. Other symptoms included nausea and vomiting which occurred with equal frequency in the two groups.

Although the lowest level of fasting blood sugar reported in any case may vary considerably because of difference in methods and circumstances under which the specimen is taken, it is interesting that in only 11 patients did the blood sugar fail to fall below 50 mg per 100 ml. Over 80 per cent had blood sugar levels below 40 mg per 100 ml (chart 5).

Among the twenty-four cases of malignant insulinoma with metastases which have been reported, four appear to have developed some or all of their hypoglycemic symptoms on the basis of extensive liver metastases rather than on that of a functioning tumor alone in that symptoms began a relatively short

time before death and no actual insulin assay was done on the tumor. This fact is emphasized because there have been reported several (141, 142) non-functioning malignant islet cell carcinomas. The embryologic explanation of this possibility has been noted in the articles by Bensley (9), Grauer (10), and Good (110).

Probably the most confusing finding in the group of patients with insulinomas is the character of the glucose tolerance test. No two investigators have conducted the tests similarly. Results vary, from flat curves to diabetic types, with the largest number, 47, starting at a low figure, rising to 100-200 mg per 100 ml and then returning to the initial low figure. In 18 patients a flat curve was found, in 21 a diabetic configuration, whereas, in 139 no test was reported. In the presence of severe hypoglycemia, oral glucose tests may be of little diagnostic value because of associated pylorospasm or pooling of the glucose solution in the stomach. Further complications in carrying out a glucose test may be met with in attempting to provide a standardized diet for two to three days prior to the test (119). Obviously frank obesity or undernutrition may also modify the glucose tolerance curve.

Too few insulin tolerance tests were reported to draw any valid conclusions, but those recorded revealed an even greater variation than was found among the glucose tolerance tests.

Obesity was reported in only 65 of the 258 patients with insulinomas. In the past this finding has been stressed but it would seem from this review to be significant only in a positive way. Only 14 per cent of the patients had hunger as a symptom. Another group found that the ingestion of food relieved other manifestations of hyperinsulinism. Among the 24 cases of malignant insulinoma obesity was noted in 9. In one patient weight was normal, three patients were thin, and the body weight was not reported in the rest. This relatively high incidence of obesity among the malignant insulinomas is interesting in view of the frequency and multitude of terminal metastases.

Diagnosis. The single most important finding in the diagnosis of insulinoma is a blood sugar value below 50 mg per 100 ml. Whipple (19) proposed in 1938 that "the characteristic syndrome evolves into a typical and essential triad of attacks of nervous or gastro-intestinal disturbances coming on in the fasting state associated with hypoglycemia with blood sugar values below 50 mg per 100 ml and immediate relief of symptoms following the ingestion of glucose." It is important to remember in regard to the third point of the triad that if a patient has been in coma for any period, he may not be aroused immediately by glucose injections. Whipple's triad, as the above points have been designated, is almost the *sine qua non* to a diagnosis of insulinoma. It should be pointed out that one not infrequently is confronted with an episodic type of illness in which the degree of hypoglycemia and the reaction to it may vary considerably from time to time. Meyer (143) has demonstrated that it is the rapidity of the fall of blood sugar that produces symptoms rather than the actual level. This may help explain the fact that more spells occur in the daytime in relation to meals than at night when the actual blood sugar level is lowest, but the low point is attained relatively slowly.

Electroencephalographic studies (124, 157) on patients with insulinomas have not been diagnostic, but do almost uniformly demonstrate high voltage, slow activity in the fasting state or with hyperventilation and with a return towards normal following glucose administration. In some patients a spike-and-dome pattern has been found, in some a tendency to localization, and in others occasional bursts of rapid activity. Hoefler et al (124) noted "no clear-cut relation between the degree of abnormality and the sugar levels" in the fasting state.

Differential diagnosis Differential diagnostic possibilities are myriad both from the viewpoint of symptoms and etiology. The group of symptomatic possibilities include brain tumor, epilepsy, alcoholism, encephalitis, neurocirculatory asthenia, cardiac neurosis, various psychoses, atypical angina pectoris, and peptic ulcer.

A comprehensive study on the etiology of hypoglycemia has been made by Conn and collaborators (53). The following is a modification of his list of differential diagnostic possibilities.

I Organic

A Hyperinsulinism

- 1 Pancreatic islet cell adenoma
- 2 Pancreatic islet cell carcinoma
- 3 Diffuse hyperplasia of islet cells

B Hepatic Disease

- 1 Infectious cholangiolitis
- 2 Toxic hepatitis
- 3 Diffuse hepatitis
- 4 Fatty degeneration or metamorphosis
- 5 Glycogenosis (von Gierke's)

C Pituitary Hypofunction (anterior lobe)

- 1 Destructive lesion (chromophobe tumor, cyst)
- 2 Atrophy and degeneration (Simmond's disease)
- 3 Thyroid hypofunction secondary to pituitary hypofunction

D Adrenocortical hypofunction (Addison's disease)

- 1 Idiopathic cortical atrophy
- 2 Destructive infectious granulomata
- 3 Destructive neoplasm

E Central nervous system lesions (hypothalamus) interference with nervous control of blood sugar

II Hypoglycemia without demonstrable anatomic lesion

A Increased secretion of insulin by normal islet cells (? autonomic balance)

B Alimentary hypoglycemia

- 1 Postgastrectomy (dumping syndrome)
- 2 Postgastro enterostomy

C Renal glycosuria

D Lactation

E Severe, continuous muscular work

F Postoperative hypoglycemia

G Severe inanition

H Factitious

I Unknown

Diffuse hyperplasia of the islets gives an identical symptomatic and laboratory picture, so that it is impossible to differentiate this lesion from an adenoma. Fortunately therapy is the same in either in that operative intervention is necessary in both. Only ten cases (21, 38, 42, 65, 144-148) of hyperplasia appear in the surgical literature.

Hepatic disease, central nervous system lesions, alimentary, renal, lactation and work hypoglycemias may all be excluded by history or simple tests. There has, however, been no adequate method to differentiate lesions of the pituitary, hypothalamus, or adrenal, although much work has been done on the relationship of these glands to the pancreas (151-154). Two simple tests are presented which may be carried out in any laboratory to determine the presence or absence of hypofunction of the anterior pituitary or adrenal cortex.

A. The subcutaneous epinephrine test for pituitary-adrenal cortical insufficiency
Principle: Epinephrine stimulates the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH). Changes in the eosinophil count act as an indicator of pituitary ACTH secretion followed by adrenal cortical activation. Compounds E and F of the adrenal cortex will depress eosinophils.

Procedure: Breakfast is held. A fasting eosinophil count is made.⁵ Then 0.3 cc. of 1:1000 epinephrine is injected subcutaneously. The patient may eat after the injection. Lunch is held until four hours later at which time the final eosinophil count is obtained.

Interpretation: A fall of fifty per cent or more in circulating eosinophils following a standard dose of epinephrine excludes hypoglycemia dependent upon serious anterior pituitary or adrenal cortical insufficiency. Normal levels for circulating eosinophils are 125-300 per cm.

B. The four-hour ACTH test. Principle: The adrenal cortex is stimulated directly by the intramuscular injection of 25 mg. of ACTH, and the eosinophil count is followed as an indicator of adrenal cortical activation.

Procedure: Same as above with the exception that 25 mg. of ACTH is injected intramuscularly.

Interpretation: A fall of fifty per cent or more in circulating eosinophils excludes adrenal cortical insufficiency.

Associated endocrine lesions. A wide variety of disturbances in other endocrine systems have been found to co-exist with insulinomas (table 6). Only nine of the endocrinopathies noted in the table were found in the 183 surviving patients, whereas, the remainder were discovered at autopsy. Only three patients had a reported family history of diabetes, while three others had been found to have diabetes mellitus before the hypoglycemia developed. Cases with complicating acromegaly have been reported by Esmarch (57) and Shelburne (81) with the third being reported by the authors elsewhere (158).

Treatment. Surgery with complete extirpation of all insulin-producing tumors is the only satisfactory method of treatment. As soon as a tentative diagnosis is

⁵ Details in preparation of diluting fluid for eosinophil counts and balanced oxalate and in technique of eosinophil count may be found in an article "Clinical Studies with Pituitary Adrenocorticotropin" by Forsham et al (155).

made and proper pre-operative preparation undertaken, surgical intervention is indicated without undue delay, because of the possibility of (1) malignant changes, (2) permanent central nervous system damage, (3) irreversibility of an attack, and (4) increasing obesity will make operative intervention more difficult. Proper and adequate pre-operative preparation presupposes an understanding of the basic metabolic difficulties in this group of patients: (1) the desirability of a high protein diet, (2) the possibility of associated potassium and phosphate depletion, (3) the necessity for improving glycogen reserves immediately prior to operation. Ether with constant intratracheal oxygen in high concentration is the ideal anaesthetic. An intravenous glucose infusion should be begun several hours prior to operation and continued until the tumor is found and removed. The blood sugar level should be followed closely during

TABLE 6

Associated endocrine disturbances reported in 258 patients with insulinoma

Toxic thyroid adenoma	5
Non toxic thyroid adenoma	3
Adrenal carcinoma	2
Adrenocortical adenoma	1
Adrenal hyperplasia	1
Hemorrhagic adrenal cyst	1
Pituitary adenoma	0
Aeromegaly	3
Basophilism of pituitary	2
Anterior pituitary hyperplasia	1
Tuberculosis posterior pituitary	1
Parathyroid adenoma	1
Parathyroid cyst	1
Thymic hyperplasia	1

and after operation. When careful exploration fails to reveal an adenoma, the consensus of opinion is that radical surgery should be performed with extirpation of over one-half of the gland (35, 115, 116, 149, 150). An excellent review article on the subject has been written by David (150). In a discussion of David's paper, Whipple pointed out the minimal physiological disturbance following even complete pancreatectomy as has been done by Priestley (35) and Whipple (106). This is the only method by which we can be positive that an adenoma has not been missed, as illustrated by Priestley's finding of a very small tumor deep in the head of the pancreas, which he removed in toto.

Other methods of treatment have included (1) a high protein, high fat and low carbohydrate diet (53), (2) pre-meal insulin (156), (3) alloxan (54, 58, 59, 118) and (4) anterior pituitary extract (137). It was hoped that alloxan might prove to be an efficacious, non-surgical treatment. Thus far three cases of islet cell metastatic carcinoma (58, 59, 118) have been treated with alloxan with temporary relief but eventual death. In each case toxic effects were so great that on several occasions therapy had to be stopped. One case of benign adenoma was

treated by Conn (54) with the unfortunate result that a permanent diabetes was produced. It is now believed that this drug damages the normally functioning islets while having very little effect on the adenomatous tissue. At present its use in therapy of insulinomas would, therefore, seem contraindicated.

Of the 200 patients operated upon there were 17 deaths or a mortality rate of 9 per cent. Of special note are the five deaths with hyperpyrexia (table 7). Whipple (22) has written that "in cases of hypoglycemia with hyperthyroidism the basal metabolic rate is apt to be lower than in other cases of Graves' disease and these patients may develop a thyroid storm. For this reason a BMR should be done in all cases of suspected islet cell tumor, and if the rate is above 15, the patient should be given a course of iodine therapy as in preparation for a thyroid operation."

From a review of these five cases as reported (20, 120-123) there is a striking resemblance to deaths with hyperpyrexia noted in patients with Addison's disease following an infusion with glucose or a glucose tolerance test. In either

TABLE 7
Causes of death postoperatively

Hyperpyrexia	5
Pneumonia	4
Cardiac failure	1
Pulmonary embolus	1
Not reported	6
Total	17

instance the explanation for these deaths is not clear, but it is obvious that patients after removal of an insulinoma present a similar situation with a state of hyperglycemia following one of hypoglycemia. This possibility serves to emphasize the necessity of intensive pre-operative dietary therapy with high caloric diets and supplementary potassium and phosphate therapy.

The actual survival time recorded is not of value in that in most cases post-operative follow up period has been brief. However, from those cases which do have a more prolonged follow up it appears that almost without exception, complete relief of symptoms for a few months after operation is tantamount to cure. Of the 183 patients surviving six had incapacitating residues from the previous hyperinsulinism and nine had minimal symptoms. Therefore, 177 patients were enabled to live a relatively normal existence and 168, or 84 per cent of all cases operated, were completely cured. Of interest were a number of patients who were thought to be irreversible mental defectives, but who became normal after operation. Another noteworthy finding is that although nearly every patient had a compensatory hyperglycemia from 1-14 days postoperatively, only two cases were reported to require insulin for more than one month post-operatively in spite of radical pancreatic resection in some instances.

SUMMARY

The 258 cases of insulinoma reported in the literature up to 1949 have been reviewed individually and the more important facts regarding incidence, pathological types, diagnosis and treatment have been summarized

The tumors may occur at any age, but predominantly in the fourth to sixth decades, and appear to be similarly distributed between males and females In contrast to popular belief the majority of tumors do not occur in the tail of the pancreas Furthermore, multiple tumors are relatively frequent These findings in addition to the increased difficulty of exploring the body and head of the pancreas probably account for many of the failures at the first operation Tumors occur occasionally in aberrant pancreatic tissue Rarely diffuse hyperplasia or adenomatosis of the islet cells is observed Only 10 per cent of tumors were shown to be definitely malignant Because of certain unusual characteristics of the tumor, a diagnosis of malignancy is often made, apparently incorrectly Whipple's "triad" of signs is a *sine qua non* for the diagnosis in most instances The bizarre nature and multiplicity of signs which may occur with hyperinsulinism delay the diagnosis in most cases, many times for periods of years Two new tests involving measurement of anterior pituitary and adrenal cortical function have been employed successfully in a case of acromegaly with two complicating insulinomas The results of surgery in most cases of insulinoma are excellent although multiple operations may be required before the tumor or tumors are successfully located and removed

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